Synthetic Applications of Nitrile Oxide/Isoxazoline Chemistry

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Declaration

I declare that this thesis was composed by myself and that it describes my own work except where specifically stated in the text. The work was carried out from October 1987 to October 1990 in the department of chemistry at the University of Edinburgh under the supervision of Dr R.M. Paton.

Ewan C. Boyd

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Postgraduate Lectures (1987-1990)

Departmental Seminars, three years attendance.

Fatty Acids and Lipids, (Prof. F.D. Gunstone) 1988, 10 lectures.

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Modern Synthetic Strategies (Dr G. Tennant) 1988, 5 lectures.

Medicinal Chemistry (Dr R.M. Paton) 1989, 5 lectures.

Medicinal Chemistry (Prof. R. Baker and Dr P. Leeson, MSD) 1989, 5 lectures.

Medicinal Chemistry (Prof. R. Baker) 1990 5 lectures.

Recent Advances in Organic Chemistry (various lecturers) 1989, 5 lectures.

Departmental German course passed (1987).

Abbreviations

Boc	*t*-butoxycarbonyl
Boc_2O	di-*t*-butyl dicarbonate
b.p.	boiling point
BuLi	butyllithium
CBZ	benzyloxycarbonyl
DIBAL	di-isobutylaluminium hydride
DMP	2,2-dimethoxypropane
DMSO	dimethylsulphoxide
ether	diethyl ether
FAB	Fast Atom Bombardment
FMO	Frontier Molecular Orbital
HMPA	hexamethylphosphoramide
HOMO	Highest Occupied Molecular Orbital
HPLC	High Pressure Liquid Chromatography
IR	Infra-red
LAH	lithium aluminium hydride
LDA	lithium di-isopropylamide
LDEA	lithium diethylamide
lit.	literature value
LUMO	Lowest Unoccupied Molecular Orbital
mmol	millimole
MO	Molecular Orbital
m.p.	melting point
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMR	Nuclear Magnetic Resonance
PCC	pyridinium chlorochromate

TFA	trifluoroacetic acid
THF	tetrahydrofuran
tlc	thin layer chromatography
Ts	tosyl (toluenesulphonyl)
TsCl	*p*-toluenesulphonyl chloride
TsOH	*p*-toluenesulphonic acid

Abstract

Three alkenes, (*R/S*)-2-phenyl-4-vinyl-4,5-dihydro-oxazole (**11**), (4*R*)-3-*N*-*t*-butoxycarbonyl-2,2-dimethyl-4-vinyloxazolidine (**12**) and (2*R*)-2-(*N*-*t*-butoxycarbonyl)aminobut-3-en-1-ol (**13**), have been prepared from (*S*)-serine and used in cycloaddition reactions with some common nitrile oxides, to investigate the effect of an allylic nitrogen at an α-chiral centre on π-facial selectivity.

Alkene (**11**) was prepared in racemic form after an unexpected racemisation during its synthesis. Cycloaddition reactions with three nitrile oxides (benzonitrile oxide, ethoxycarbonylformonitrile oxide and bromonitrile oxide) furnished the isoxazoline/oxazoline adducts in poor to good yield. π-facial selectivity varied from 69:31 (BrCNO) to 82:18 (EtO_2CCNO) in favour of the (5*R*,4'*S*) *erythro* product. The stereoselectivity has been explained by both a steric transition state model and by the existence of a stereoelectronic contribution to the stability of the transition state.

Alkene (**12**) afforded good yields of cycloadducts with the same three nitrile oxides, but only gave moderate π-facial selectivity (*ca.* 66:34); the (5*R*,4'*S*) *erythro* products were again favoured. The diastereomeric products were separated after partial deprotection of the β-amino-alcohol moiety (deacetonisation). The observed π-facial selectivity has been explained by a steric transition state model.

The *N*-protected vinylamino-alcohol (**13**) has been reacted with benzonitrile oxide and ethoxycarbonylformonitrile oxide to give the corresponding cycloadducts in moderate yield. π-facial selectivity was poor, and the (5*S*,2'*S*) *threo* isomer was favoured. The reduction and

reversal of π-facial induction has been explained by a hydrogen bonding interaction in the transition state.

Two examples of chiral heterocyclic nitrile oxides **(39)** and **(41)** which correspond to the two heterocyclic alkenes have also been prepared, each of which represents a protected chiral β-amino-alcohol nitrile oxide.

(4*R*)-3-*N*-*t*-butoxycarbonyl-2,2-dimethyloxazolidine-4-carbonitrile oxide **(39)** was generated from the corresponding oxime **(40)** and reacted with three olefins: styrene, oct-1-ene and diethylfumarate, affording the cycloadducts in poor to good yield.

(*R/S*)-2-phenyl-4,5-dihydro-oxazole-4-carbonitrile oxide **(41)** was generated by dehydration of the corresponding nitromethyl heterocycle **(42)** and reacted, when formed in a low steady state concentration, with styrene and oct-1-ene to give moderate yields of the bis-heterocyclic adducts. When the concentration of the nitrile oxide was not controlled by the slow addition of the precursor, the diastereomeric furazan-*N*-oxides **(45a & b)** were the only isolated products. Isomer ratios for both nitrile oxides were *ca.* 1:1.

Finally, five examples of isoxazole- and isoxazoline-3-aldoximes have been prepared, and conditions established for their conversion to the corresponding 3-carbonitrile oxides. *In situ* generation with sodium hypochlorite and *N*-chlorosuccinimide/triethylamine proved most successful. A series of bi-isoxazoles, isoxazole/isoxazolines and bi-isoxazolines have been prepared in moderate yield as potential lubricant additives.

Contents

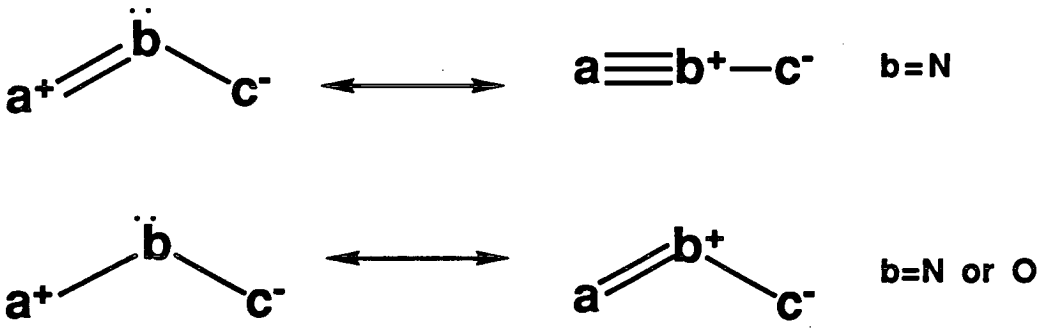
2 Results and Discussion

1. Introduction

1.1. 1,3-Dipoles

The category of compounds known as 1,3-dipoles was first classified by Huisgen in 1958.[1] They are defined as a three atom π-electron system, over which is delocalised four π-electrons.[2] Such systems are isoelectronic with the allyl anion.

The traditional representation of the 1,3-dipolar structure, a^+-b-c^-, is drawn such that atom **a** posseses an electron sextet, while atom **c** provides an unshared pair of electrons. Although compounds with an electron sextet on carbon, oxygen or nitrogen are unstable, in 1,3-dipolar systems stabilisation is possible if the central atom **b** is capable of donating a pair of electrons, thus establishing an all octet resonance hybrid[3] (scheme 1).

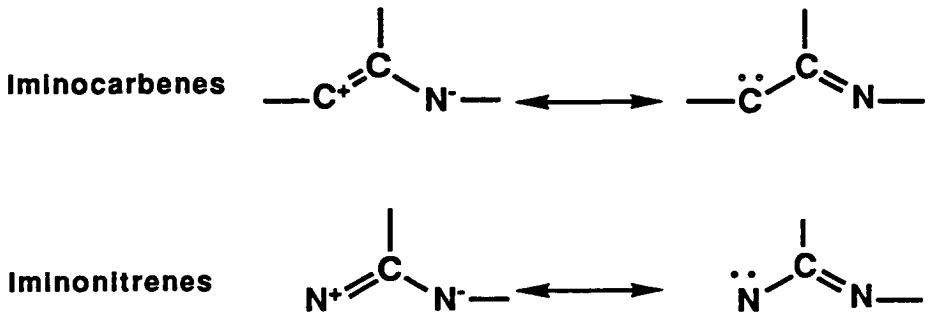


scheme 1

If the central atom is carbon, octet stabilisation is impossible and so 1,3-dipoles of this type are highly reactive short lived spieces, often displaying reactions of carbenes and nitrenes (scheme 2).

It is important to note that the term 1,3-dipole does not imply any formal localisation of charge at these positions; instead it reflects the propensity of the species to undergo cycloaddition reactions with unsaturated

systems *via* these termini. Experimentally determined dipole moments thus tend to be much lower than those which are calculated, reflecting the effective charge delocalisation through the π-system[4] (table 1).

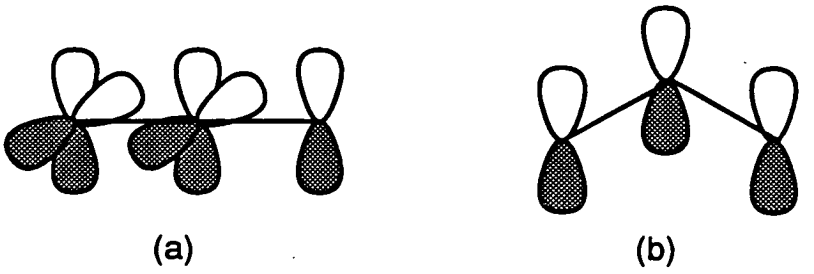


scheme 2

Table 1. Calculated and experimentally determined dipole moments

	Propargyl	Allenyl	Experimental
Diazomethane	$N\equiv N^+-C^-H_2$ 6.2 (→)	$N^-=N^+=CH_2$ 5.5 (←)	$N\equiv N=CH_2$ 1.5 (←)
Hydrogen Azide	$N\equiv N^+-N^-H$ 6.0 (→)	$N^-=N^+=NH$ 5.4 (←)	$N\equiv N=NH$ 0.85 ( )
Fulminic Acid	$HC\equiv N^+-O^-$ 5.7 (→)	$HC^-=N^+=O$ 5.6 (←)	$HC\equiv N=O$ 3.15 (→)

1,3-Dipoles can be divided into two separate classes, those which posses an orthogonal π-bond (propargyl-allenyl anion type) and those which do not (allyl anion type) (fig. 1). Some examples of the two different categories (which have oxygen and nitrogen centres) are shown in table 2.[5]

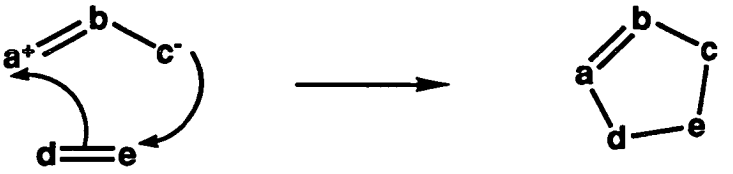


(a) (b)

Fig. 1 Types of 1,3-dipoles: (a) with, and (b) without an orthogonal double bond.

1.2. 1,3-Dipolar Cycloaddition Reactions

A 1,3-dipolar cycloaddition reaction is the coupling of a 1,3-dipole with a multiple bond system, the dipolarophile, to form a five membered heterocyclic ring (scheme 3). A variety of multiple bond systems can act as dipolarophiles eg C=C, C=N, C=S, C≡C, C≡N.



scheme 3

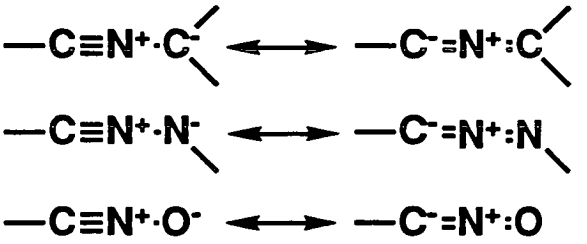
1.2.1. Mechanism

The mechanism of 1,3-dipolar cycloaddition reactions has been the subject of much controversy over the past 30 years. Firestone[6-9] proposed and defended a two step mechanism (scheme 4, path A) involving a discrete spin-paired diradical intermediate, while Huisgen[10-13] championed the concerted process involving no intermediate, with simultaneous, but not necessarily synchronous, formation of the two new

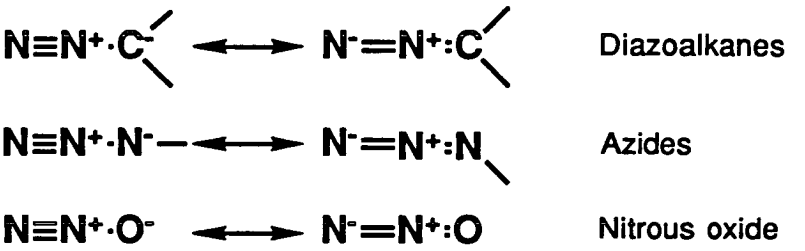
Table 2. Some common 1,3-dipoles

Propargyl-allenyl type

Nitrilium betaines

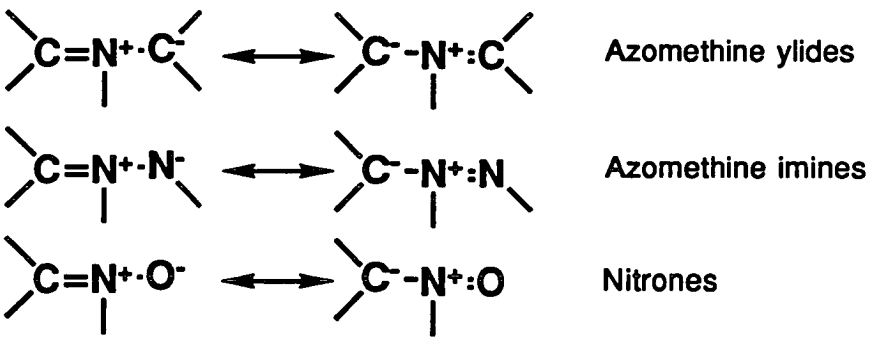


Diazonium betaines

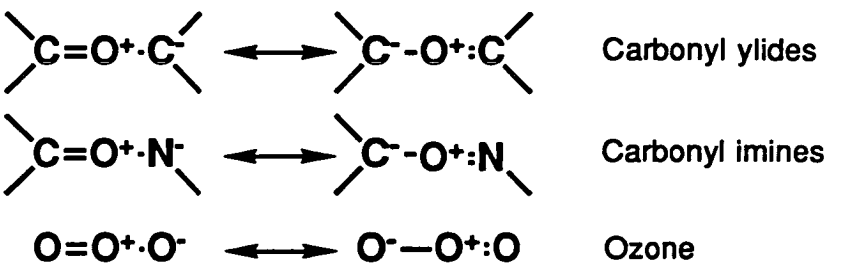


Allyl anion type

With central nitrogen

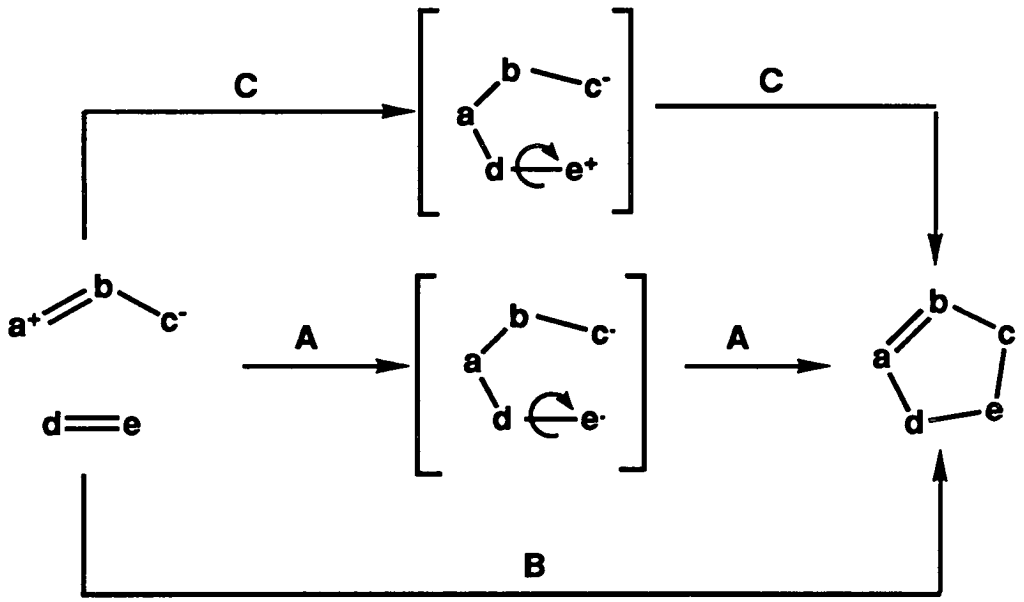


With central oxygen



σ-bonds (scheme 4, path B).

A two step process involving a zwitterionic intermediate (scheme 4, path C) in which the two new σ-bonds are formed in a stepwise manner has been rejected on the grounds that there is very little difference in the reaction rate for non-polar and polar solvents. A greater rate would be expected in polar solvents, due to enhanced stabilisation of the charged intermediate. The observed stereospecificity of 1,3-dipolar cycloaddition reactions also casts doubt on the zwitterionic mechanism,[14] since rotation about the d-e bond would result in the loss of the dipolarophile stereochemistry in the cyclic product.



scheme 4

Huisgen[15 16] has shown that the zwitterionic process is not the general mechanism for 1,3-dipolar cycloadditions by demonstrating that it can only operate in extreme cases. Thiocarbonyl ylides were chosen because of their very high π-molecular orbital (MO) energies, approaching those of the allyl anion, along with an electron de ficient

dipolarophile, dimethyldicyanofumarate **(2)** which has very low π-MO energies. The reaction is thus very strongly dipole-HOMO controlled, rendering the energy contribution from the formation of the second bond so low that it can no longer account for the large negative entropy of activation (Fig.2) ; this forces the reaction into a zwitterionic mode with a resulting loss of stereochemistry in the products. Reaction of thiocarbonyl ylide **(1)** with the *trans*-alkene dimethyldicyanofumarate **(2)** afforded *cis*-adduct **(3)** as well as the *trans*-product **(4)** (scheme 5).

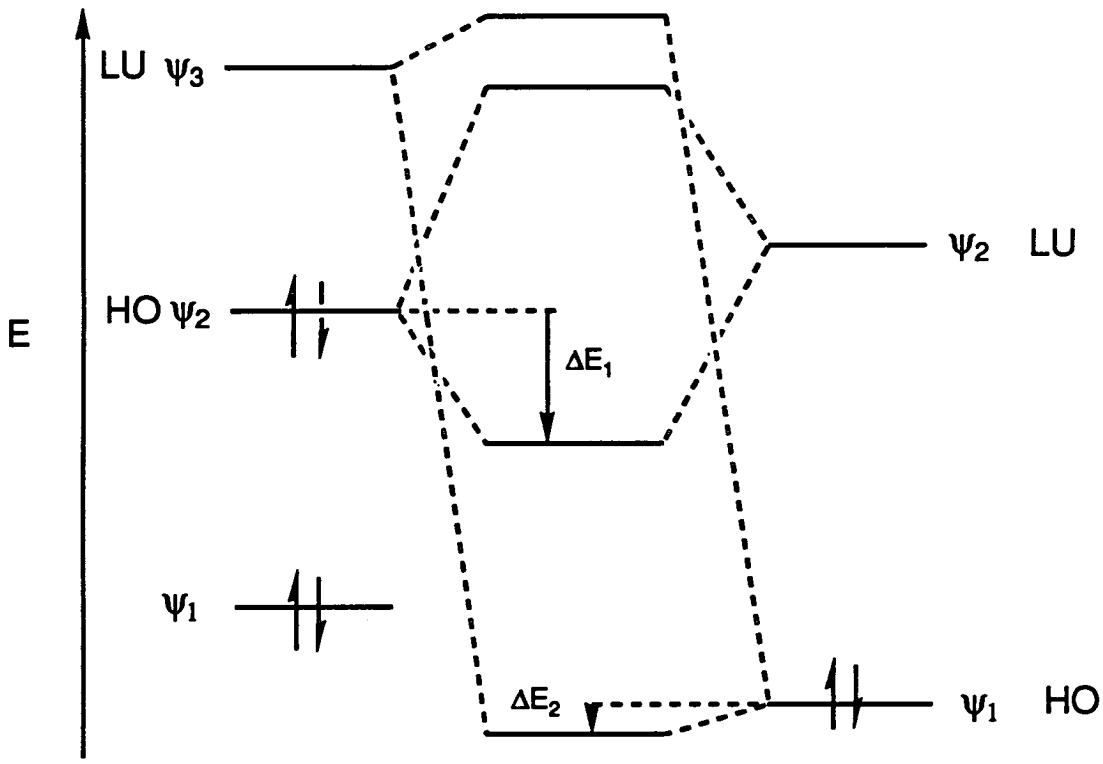
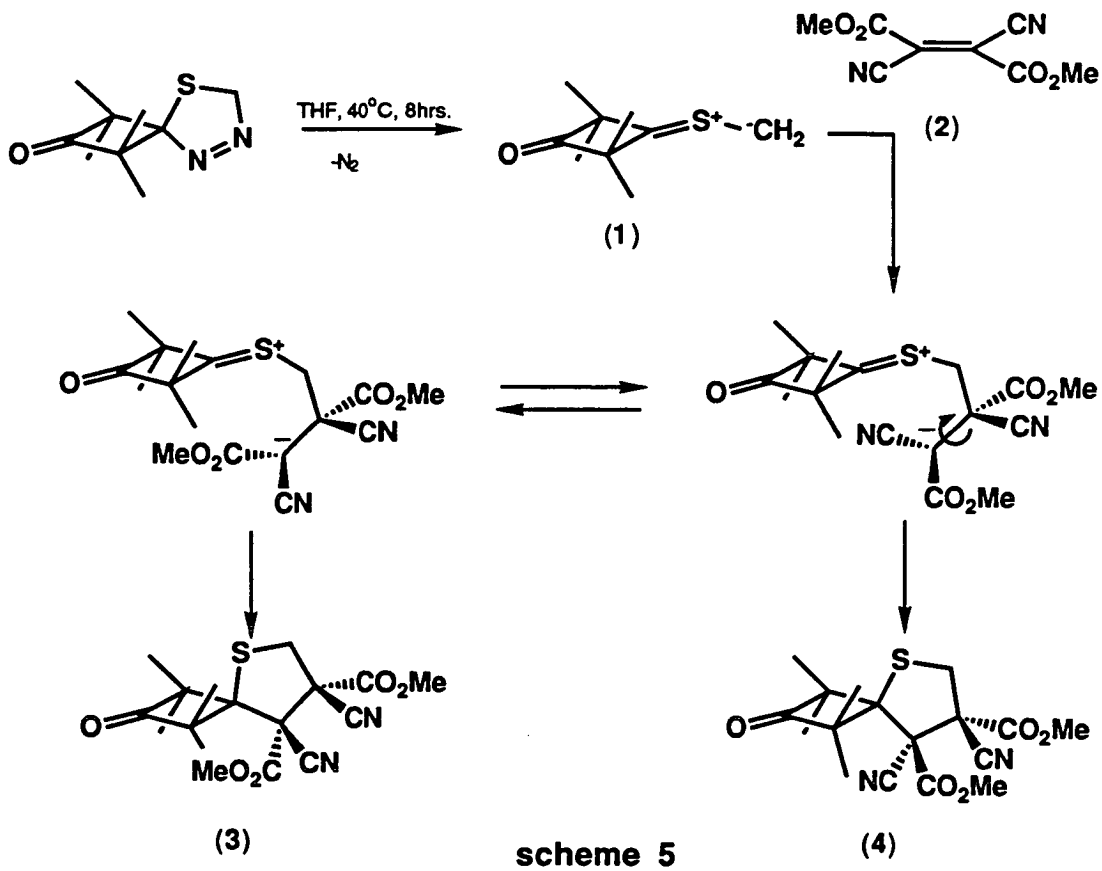


Fig.2 π-HO-LU interaction for a strongly dipole-HO controlled reaction showing the small energy contribution from the formation of the second σ-bond.



scheme 5

1.2.2. Concerted versus Diradical

As has been previously mentioned, this aspect of 1,3-dipolar chemistry has been the subject of heated debate over the past two decades. The main argument for the concerted process is based on the stereospecificity which is observed in these reactions. This is consistent with a system which obeys the Woodward-Hoffmann rules for the conservation of orbital symmetry.[14]

Huisgen[12] argues that the retention of alkene stereochemistry in the cyclic adduct can only be explained by a concerted process in which both of the new σ-bonds are being formed at the same time, even if they are not equally advanced. This mechanism which requires a highly ordered transition state would also explain the large negative entropies

of activation which are observed for these reactions.

Firestone has countered that the stereospecificity could equally well be explained by a two step sequence, if the spin-paired diradical intermediate has a greater activation energy for a single bond rotation than the barrier to ring closure[6] (scheme 4, path A). This argument is extended to address the entropy question; the explanation being that a highly orientated intermediate is required for ring closure to occur, if this requirement is not satisfied then dissociation to reactants will provide an alternative path.

It is further contended by Firestone[6] that for acetylenic dipolarophiles an enhancement of rate would be expected with respect to analogous olefins as a result of the formation of an aromatic ring, a portion of the aromatic stability being present in the transition state. This is not in fact observed, acetylenes being generally less reactive. He claims that this is an argument for a two step process in which the formation of the aromatic nucleus is delayed until after the rate determining step.

Huisgen responded by proposing that the transition state for the concerted process resembles an orientation complex, and as such is not planar (Fig. 3); profit from the aromatic stabilisation cannot be realised until the middle atom of the 1,3-dipole moves towards the plane of the ring.

The regioselectivity of these reactions was for a while considered to be a strong argument for a diradical mechanism, however, frontier molecular orbital (FMO) theory provides a good explanation for the observed outcome of these reactions, based on the polarisation of the frontier molecular orbitals (see sect. 1.2.4).

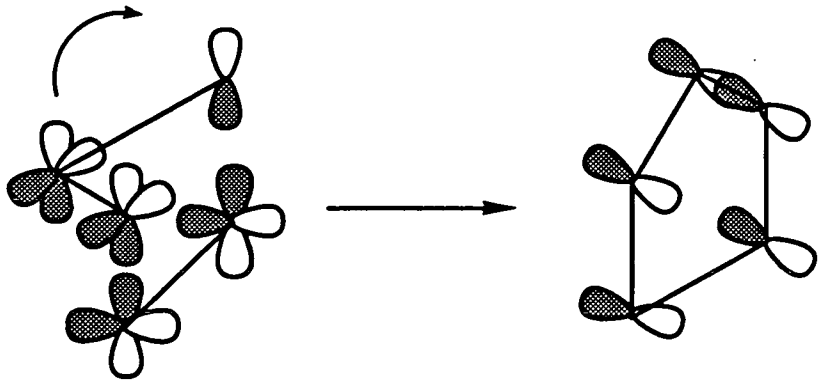


Fig. 3

1.2.3 Reactivity

While the Woodward-Hoffmann rules can be used to explain the mechanism of 1,3-dipolar reactions, they do not allow any assessment of reaction rates to be made.

The rate of a cycloaddition reaction is proportional to the stabilisation energy gained on formation of the transition state. This in turn is proportional to the square of the area of overlap of the interacting FMOs, and inversely proportional to the energy separation of those orbitals. Thus, the smaller the energy gap between an interacting pair of FMOs the greater is the energy of stabilisation (Fig. 4).

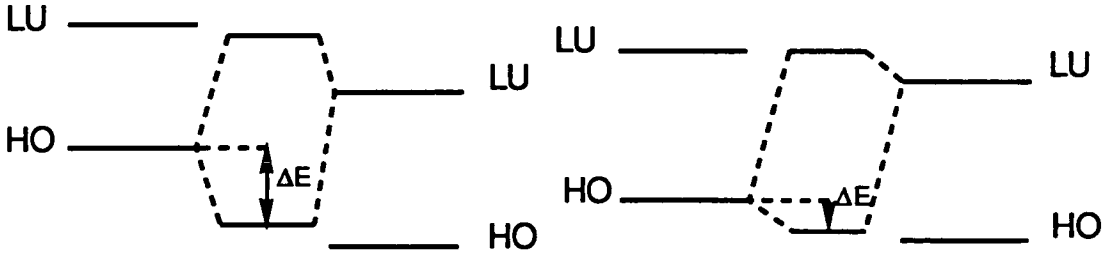


Fig. 4

With this simplified model and the limiting scenarios arrived at by Sustmann[17-19] (Fig. 5), it is possible to rationalise the observed reactivities of 1,3-dipoles and the effect of substituents on both of the reacting fragments.

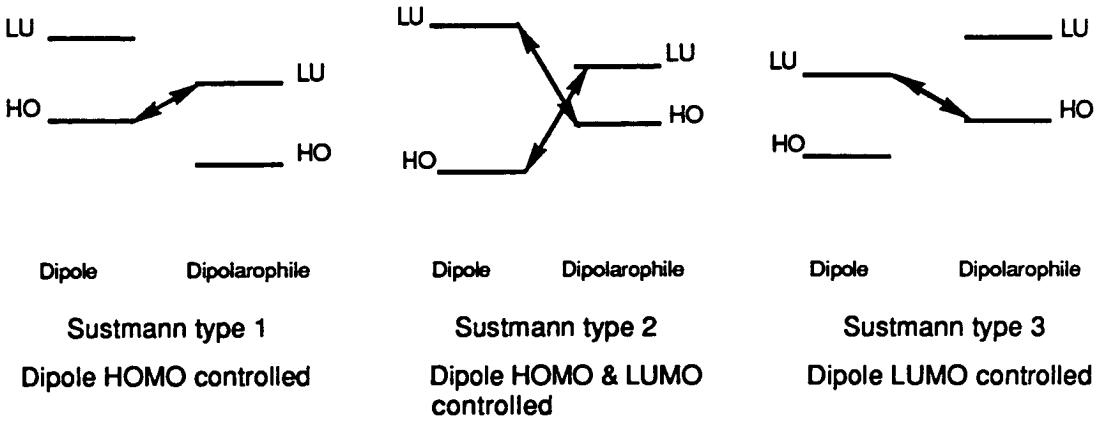


Fig. 5

It now becomes apparent that for Sustmann type 1 systems (dipole HOMO controlled), conjugating and donating substituents on the dipole and conjugating and withdrawing groups on the dipolarophile will enhance reaction rates, while the reverse is true for Sustmann type 3 systems (dipole LUMO controlled). The reaction rates of Sustmann type 2 systems are enhanced by donating, withdrawing, and conjugating substituents.

1.2.4 Regioselectivity

In 1968 Huisgen[12] suggested that the regioselectivity of Diels-Alder and 1,3-dipolar cycloaddition reactions represented one of the major unsolved problems in the area. As for many other facets of this field of chemistry, FMO theory provided a credible explanation.

The non-symmetrical nature of 1,3-dipoles and substituted dipolarophiles

means that the magnitude of the coefficients of each molecular orbital are not equal as is the case for ethylene (Fig, 6).

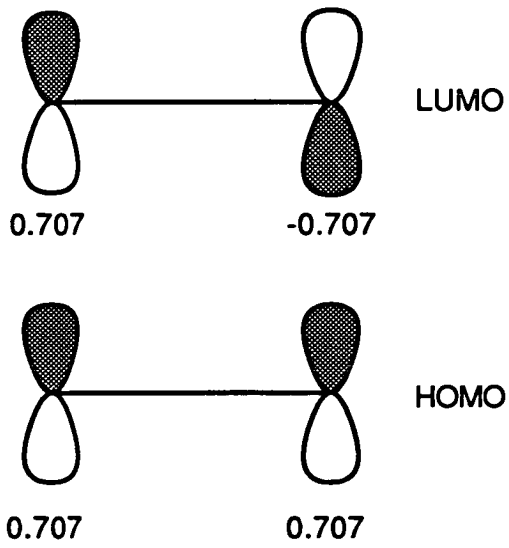
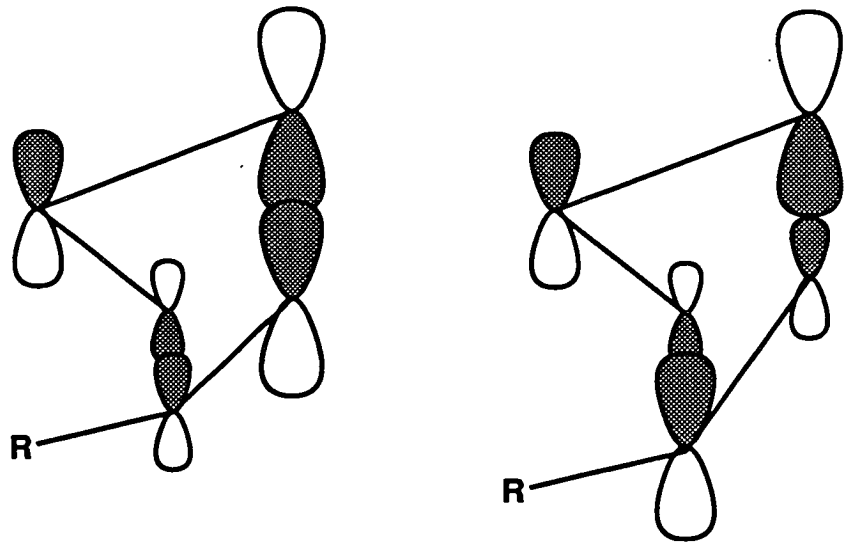


Fig. 6 Coefficients of ethylene

For a pair of interacting FMOs it is most favourable for orbitals with large coefficients to combine and for orbitals with small coefficients to interact with each other (Fig. 7). Thus a knowledge of orbital coefficients and FMO energies for dipoles and dipolarophiles, many of which have been calculated,[20 21] allows the dominant interaction to be determined and therefore the regiochemistry of the adduct to be predicted.

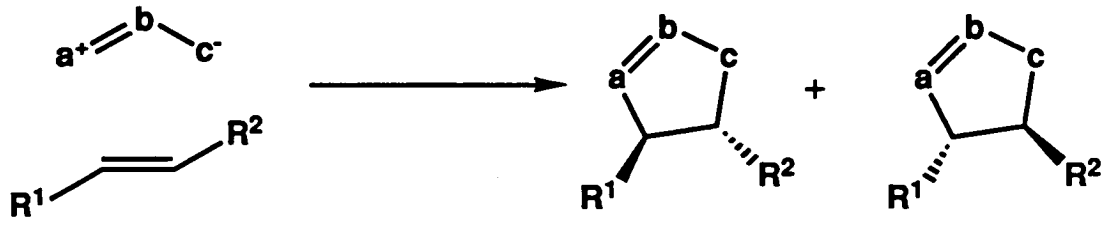


Favoured Disfavoured

Fig 7.

1.2.5 Stereoselectivity

The stereoselectivity of 1,3-dipolar cycloaddition reactions is one of the most potent arguments for a concerted mechanism (sect. 1.2.1 and 1.2.2). When 1,3-dipoles combine with 1,2-disubstituted olefins, the stereochemistry of the dipolarophile is carried through to the heterocyclic adduct (scheme 6). This is one of the factors which makes this type of reaction synthetically important for many dipoles.



scheme 6

1.3. Nitrile Oxides

1.3.1. History

The parent nitrile oxide, fulminic acid ($HC\equiv N^+-O^-$) was prepared as early as 1800,[22] while probably the most widely used member of the series, benzonitrile oxide ($PhC\equiv N^+-O^-$) was first reported in 1886.[23] Cycloaddition reactions of nitrile oxides with alkenes were first discovered by Quilico around 1950. Later the pioneering work of Huisgen led to much greater understanding of these reactions.

In the 1970s a great deal of attention was focused on the theoretical aspects of nitrile oxide cycloaddition chemistry, and the work of Houk[20 21] and Sustmann[17-19] allowed the observed reactivity and regiochemistry to be explained.

During the next decade attention turned to the use of nitrile oxide/isoxazoline chemistry as a synthetic route to a variety of acyclic functionality; most prominent in this field are the names of Curran,[24] Jager,[25 26] Kozikowski,[27] and Torssell.[28] This in turn led to the investigation of asymmetric induction in cycloaddition reactions of nitrile oxides with chiral alkenes.

1.3.2. Electronic Structure

Nitrile oxides are members of the propargyl-allenyl subset of 1,3-dipoles, possessing an orthogonal π-bond. Their structure can be represented by a series of resonance hybrids (Fig. 8). The heteropropargyl and heteroallenyl structures, **a** and **b**, are the only canonical forms in which all atoms possess a full octet of electrons, and are considered to be the most important contributors to the overall electronic picture of these 1,3-dipoles. **c** and **d** show the typical 1,3-dipolar structures.

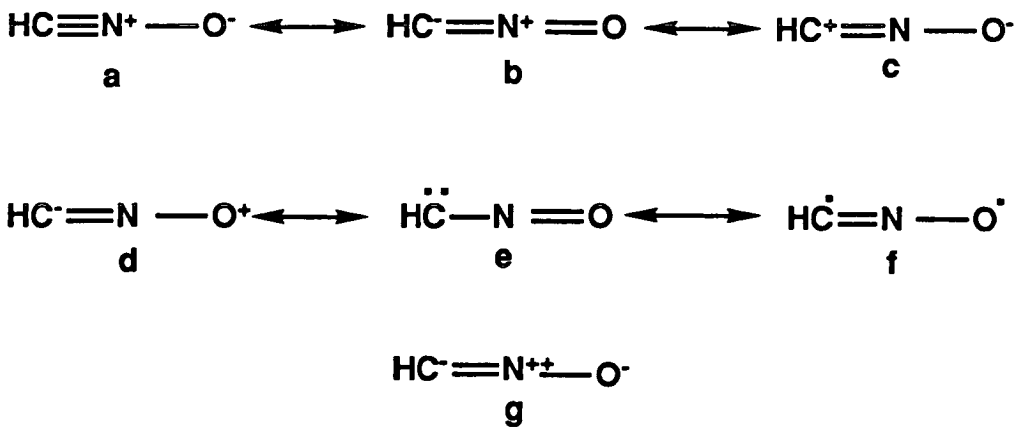


Fig 8

1.3.3. Generation

Cycloaddition reactions with nitrile oxides are most commonly carried out with the dipole being generated *in situ* in the presence of the dipolarophile. Regardless of the source of the nitrile oxide, reactions are usually structured to allow slow generation of the intermediate, thus maintaining a low steady state concentration and minimising competing dimerisation to the furoxan (furazan-*N*-oxide) (scheme 7).

Two methods of nitrile oxide formation find widest usage: oxidation of aldoximes and dehydration of primary nitroalkanes. A few other less generally applicable procedures have also been developed; these are mentioned at the end of this section.

1.3.3.1. Oxidation of Aldoximes

Oxidation of aldoximes to nitrile oxides is most often a two step sequence, involving initial chlorination to the hydroximoyl chloride followed by dehydrochlorination (scheme 7). In early work chlorination was achieved by treatment of the aldoxime in an inert solvent at low temperatures with chlorine gas.[29] This procedure is still used, however, this imposes limitations on the nature of the functionality which the

aldoxime and ultimately the nitrile oxide can carry. With this methodology the aldoxime cannot possess unsaturation,[30] ketones,[31] and some aromatic rings.[30] [32] For example thiophen-2-aldoximes afford, on treatment with chlorine, 5-chlorothiophen-2-hydroximoyl chloride.[33]

Many milder chlorinating procedures have since been developed to widen the scope of this route; nitrosyl chloride[33] [34] has been used as a selective chlorinating agent, as have sodium hypochlorite[35] and sodium hypobromite.[36] The latter two reagents combine the halogenation and dehydrohalogenation steps, and allow sensitive functionality such as double bonds to survive intact.

N-bromosuccinimide[37] (NBS) and *N*-chlorosuccinimide[38-40] (NCS) have both been used to halogenate aldoximes even in the presence of alkenes, various heterocycles and methoxylated aromatic rings.

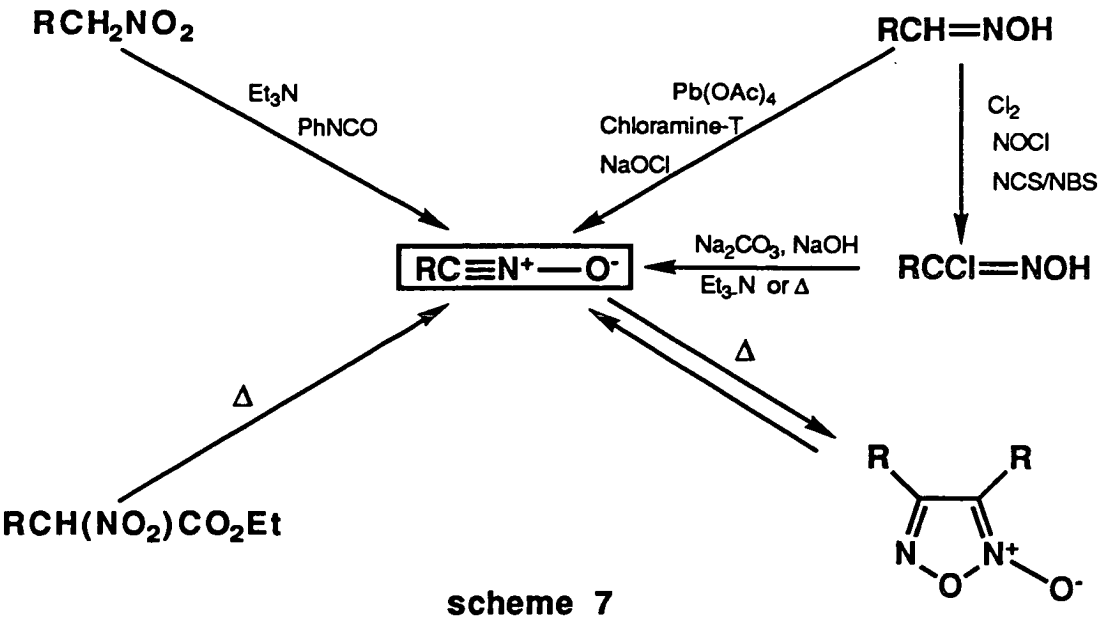
Recently nitrile oxide cycloadditions have been carried out using chloramine-T to generate the dipole directly from the aldoxime.[41] This conversion is thought to proceed by chlorination of the oxime followed by base catalysed dehydrochlorination.

Bases which have been employed for the dehydrochlorination step include sodium carbonate[3] or sodium hydroxide in a two phase system. However, these have now been superseded by triethylamine[42] [43] which is added slowly in an organic solvent.

Lead tetraacetate has been used for the direct convertion of *syn*-aldoximes to nitrile oxides.[44]

1.3.3.2. Dehydration of Primary Nitroalkanes (Mukaiyama's Method)

Primary nitroalkanes are dehydrated in the presence of isocyanates with



scheme 7

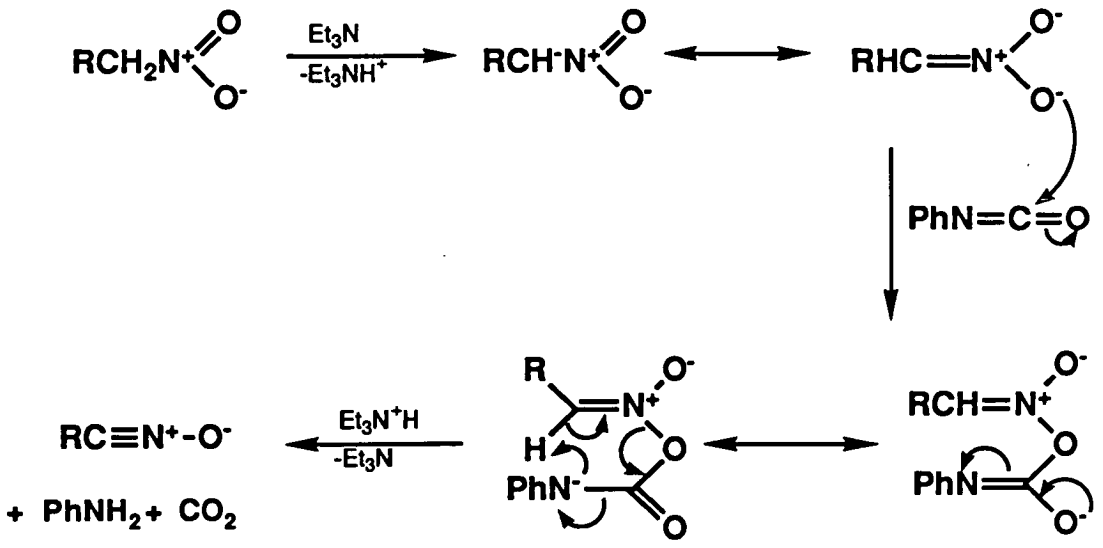
catalytic quantities of triethylamine to afford nitrile oxides.[45] This method accommodates a wide range of functionality although primary and secondary alcohols must be protected to avoid reactions with the isocyanate. The ready accessibility of primary nitro alkanes makes this a very important route to nitrile oxides.

The mechanism of this reaction (scheme 8) is believed to involve initial abstraction by base of an α-hydrogen followed by reaction of the resulting nitronate anion with the isocyanate.

1.3.3.3. Other Methods of Generation

An alternative, but less generally applicable, approach to nitrile oxides is that developed by Shimizu.[46-48] Nitrile oxides bearing ethoxycarbonyl, aminocarbonyl and alkyl substituents have been generated by thermolysis of the appropriate nitroacetates in refluxing mesitylene. The proposed mechanism is shown in scheme 9.

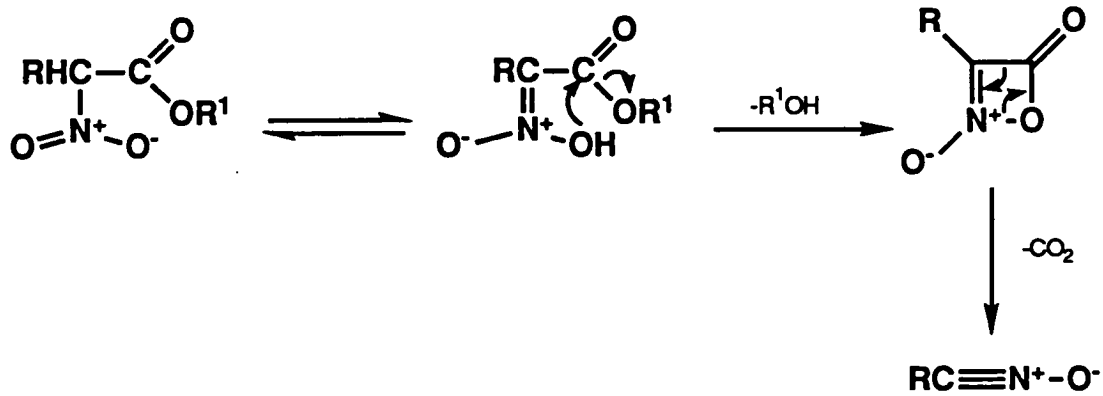
Thermolysis of hydroximoyl halides in an inert solvent has been used to



scheme 8

generate nitrile oxides in low steady state concentrations.[49-51] This methodology takes advantage of the equilibrium between hydroximoyl halides and the nitrile oxide and hydrogen halides.

Furoxans have also been subjected to thermolysis in refluxing solvents to provide a source of these 1,3-dipoles by cycloreversion.[52-54] The temperature required is dependent on the nature of the substituents (scheme 7).

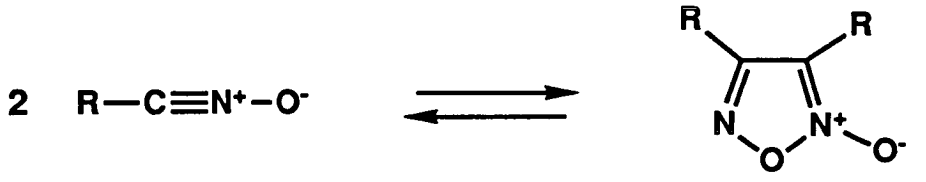


scheme 9

1.3.4. Reactions

1.3.4.1. Dimerisation

Nitrile oxides when generated in the absence of a trapping speices usually dimerise to give furoxans (scheme 10). The rate of dimerisation is variable and depends on the electronic and steric influence of the substituents. Many sterically hindered nitrile oxides can be isolated and stored indefinitely,[55] whereas electron deficient analogues are prone to very rapid dimerisation.



scheme 10

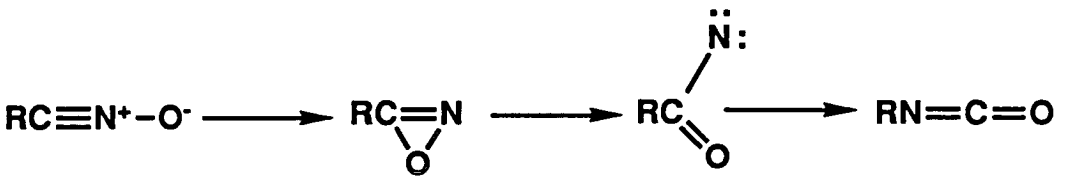
Furoxan formation often occurs as a side reaction in cycloaddition reactions, necessitating careful experimental design to minimise its occurrence.

Aromatic nitrile oxides can undergo an alternative dimerisation to 1,2,4-oxadiazole-4-oxides (scheme 11). This usually happens under the influence of acid catalysis.

scheme 11

1.3.4.2. Rearrangement to Isocyanates

Nitrile oxides can undergo a photochemical or thermal rearrangement to isocyanates.[55] Thermally the process occurs between 110-140°C, but is only cleanly observed when the nitrile oxide is resistant to dimerisation. Theoretical investigation of this reaction[56] suggests that it proceeds by the sequence shown in scheme 12.



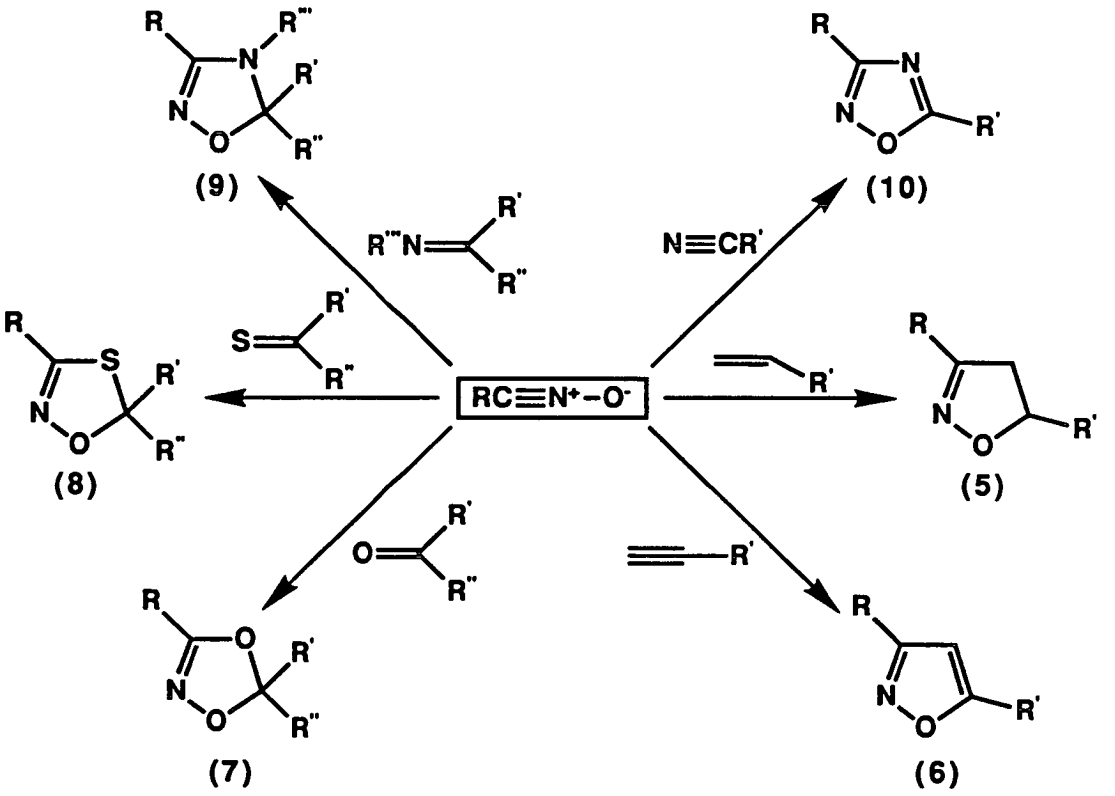
scheme 12

1.3.4.3. Cycloaddition Reactions (scheme 13)

1.3.4.3.1. With Alkenes

Nitrile oxides undergo 1,3-dipolar cycloaddition reactions with alkenes affording 2-isoxazolines (4,5-dihydroisoxazoles) **(5)**. The reactivity of the dipolarophile is enhanced by both electron withdrawing and donating substituents. Mono- and 1,1-disubstituted olefins undergo this reaction with, in most cases, complete regiospecificity yielding the 5-substituted-2-isoxazoline, while 1,2-disubstituted alkenes tend to form mixtures of regioisomers. 1,1,2-tri- and 1,1,2,2-tetra-substituted alkenes are much less reactive.

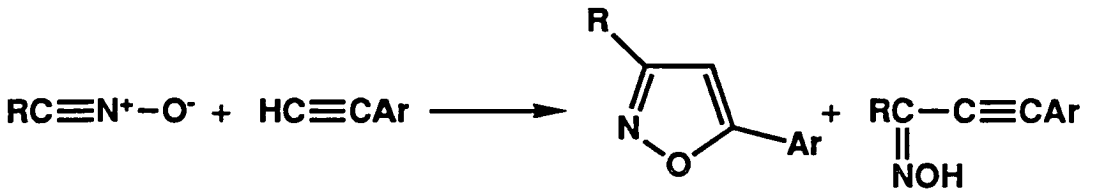
One of the most important features of this type of reaction is its stereospecificity; 1,2-disubstituted alkenes undergo cycloaddition with complete retention of dipolarophile stereochemistry. The relative stereochemistry of the saturated carbons in the heterocyclic product is therefore determined by the geometry of the olefin.



scheme 13

1.3.4.3.2 With Alkynes

Cycloaddition reactions of nitrile oxides with alkynes afford isoxazoles **(6)**, the aromatic analogues of 2-isoxazolines. Monosubstituted alkynes give mainly the 5-substituted heterocycles; however, these dipolarophiles show a greater propensity to form the 4-substituted ring than does the corresponding alkene. Acetylenic dipolarophiles also show a lower reactivity towards cycloaddition, and in the case of aryl alkynes there is the additional complication of competing 1,3-addition products[57] (scheme 14).



scheme 14

1.3.4.3.3. With Carbon-Heteroatom Multiple Bonds

1.3.4.3.3.1. With Carbonyls and Thiocarbonyls

Aliphatic aldehydes and ketones react with nitrile oxides to give 1,3,4-dioxazoles (**7**) only in the presence of Lewis acid catalysts such as BF_3-etherate.[58] More activated carbonyl compounds such as aromatic aldehydes undergo this reaction in the absence of catalyst.[59]

Thiocarbonyl dipolarophiles show good reactivity towards nitrile oxides.[60] [61] The products, 1,4,2-oxathiazolines (**8**), undergo a thermal decomposition reaction affording isothiocyanates and the carbonyl equivalent of the dipolarophile, thus providing a method of converting thiocarbonyls to carbonyls.[60] [62]

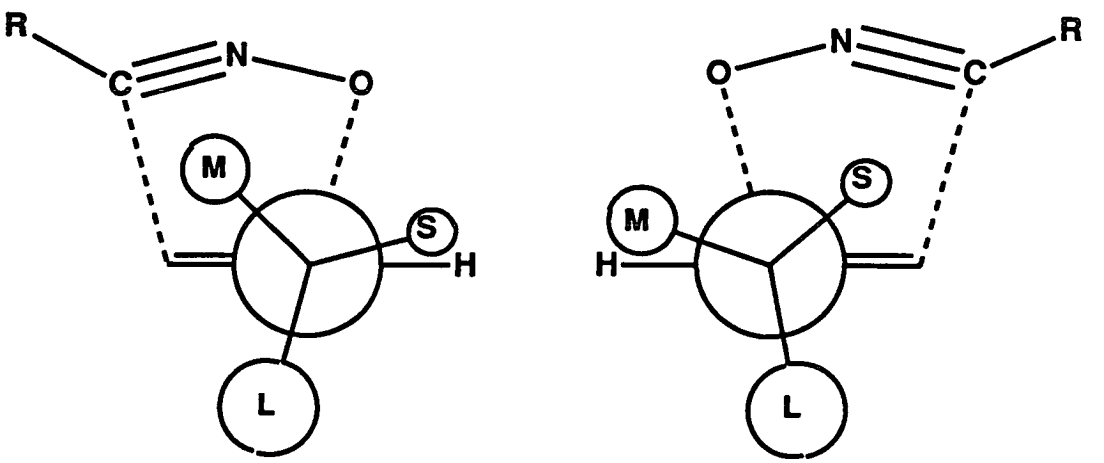
1.3.4.3.3.2. With Imines and Nitriles

Both aliphatic[63] and aromatic[64] imines show good reactivity towards nitrile oxides, affording high yields of 1,2,4-oxadiazolines (**9**). The nitrile group is considerably less reactive, and while aromatic, heteroaromatic and electron-deficient nitriles give reasonable yields of 1,2,4-oxadiazoles[63] [65] (**10**), aliphatic nitriles require activation with BF_3-etherate.[58]

1.4. Asymmetric Induction in Nitrile Oxide Cycloaddition Reactions

During the past twenty years a great deal of attention has been focused on nitrile oxide cycloaddition chemistry, fuelled mainly by the potential source of acyclic functionality provided by the resultant 2-isoxazolines.[66] [67] This in turn has prompted interest in π-facial selectivity in the cycloaddition step, which would provide stereoselective routes to acyclic compounds.

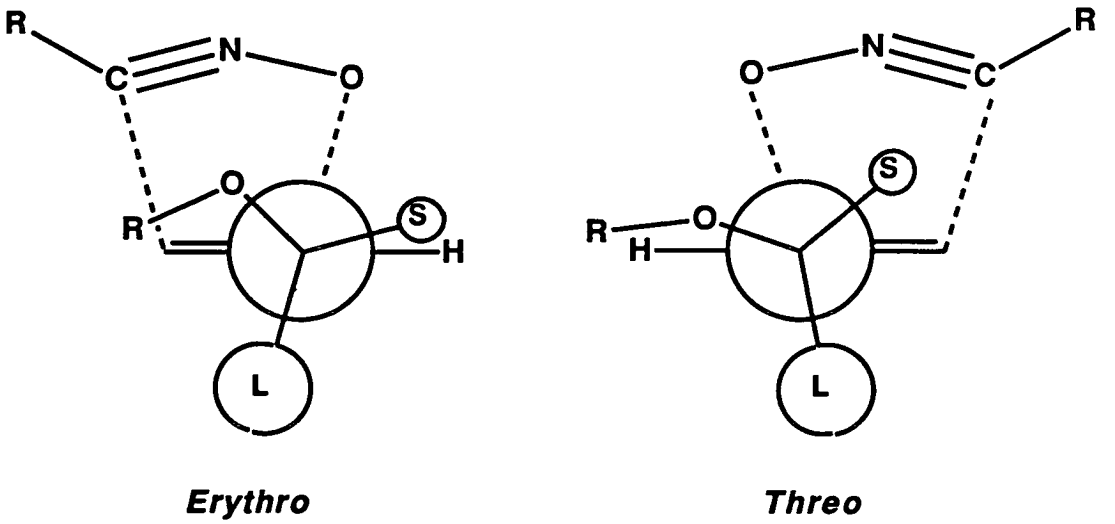
Much of the theoretical rationalisation of nitrile oxide cycloadditions with alkenes possessing a chiral allylic substituent has been provided by Houk.[68-72] These computational studies, which are supported by experimental evidence, suggest that the vicinal substituents in the transition state are staggered with respect to the forming C-O bond, with the largest group taking up the antiperiplanar conformation (Fig. 9). The major product arises from transition state **A** in which the medium substituent is in the less sterically demanding "inside" position. The diastereomer ratio increases as the size of the large group is increased.[72] The minor product arises from transition state **B**.



Major A **Minor B**

Fig. 9

Especially high selectivity has been observed in nitrile oxide cycloaddition reactions with chiral allylic ethers.[71 73] This is explained by the "inside alkoxy effect". The major *erythro* isomer is formed *via* the transition state in which the large group, as before, is in the antiperiplanar position with respect to the forming C-O bond, and the alkoxy group takes up the "inside" position (Fig 10).



Erythro ***Threo***

Fig. 10

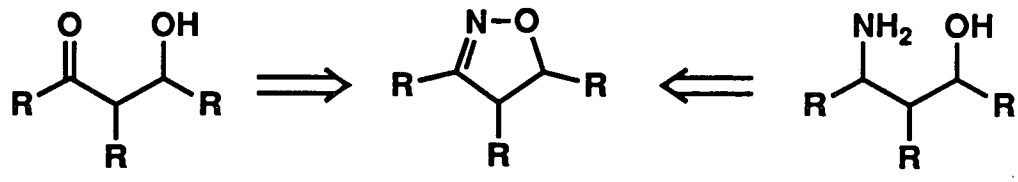
The *erythro-threo* ratio increases as the large group becomes more bulky. This is proposed to result from an increase in the C=C-C-L dihedral angle which in turn brings the ethereal oxygen into closer proximity to the nitrile oxide oxygen in the transition state which leads to the *threo* product. It is also proposed that the alkoxy group avoids the *anti* position in order to minimise electron withdrawal from the electron deficient transition state by overlap of the $CO\sigma^*$ orbital with the π-system.[71]

Cycloaddition reactions involving chiral nitrile oxides with achiral alkenes have also been investigated and have been found to give very poor

π-facial selectivity.[74-76] This is thought to be a result of the remoteness of the existing asymmetric centre from the forming one.

1.5. Ring Opening Reactions of 2-Isoxazolines

Much of the current interest in nitrile oxide/isoxazoline chemistry is directed towards the functionality which is masked by the heterocyclic ring. The two most important systems which are available are from these rings are γ-hydroxyamines and β-hydroxyketones from which α,β-unsaturated ketones are accessible (scheme 15).



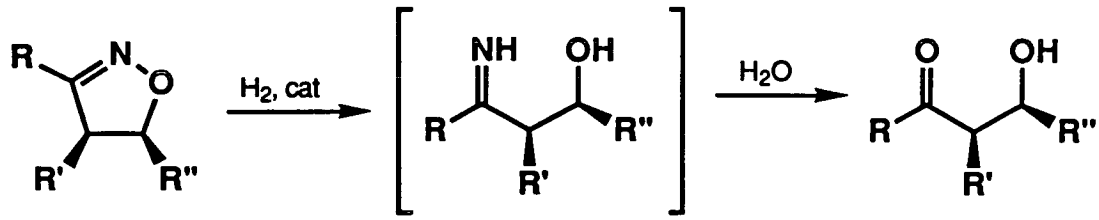
scheme 15

The features of 2-isoxazolines which make them particularly suitable for the role of synthetic equivalents are: their accessibility *via* 1,3-dipolar cycloaddition reactions, the absolute transcription of olefin stereochemistry to the heterocycle, the stability of the ring system to a variety of conditions and the lability of the N-O bond to mild reagents. This allows the isoxazoline ring to be constructed at an early stage in a synthetic pathway and then unmasked at an appropriate time.

1.5.1 β-Hydroxyketones

The most widely used method of generating β-hydroxyketones from 2-isoxazolines is catalytic hydrogenolysis (scheme 16). These reactions are usually carried out in an aqueous methanol mixture with either Raney

nickel or palladium on activated charcoal as the hydrogenation catalyst. Boric acid[77] now seems to have gained widespread acceptance as the reagent of choice for promoting hydrolysis of the β-hydroxyimine intermediate. Other reagents which have been used for this purpose with varying degrees of success include: acetic acid,[78] concentrated HCl,[79] aluminium trichloride,[79] boron trichloride,[80] acetate buffers,[77] phosphate buffers,[77] and trimethyl borate.[77]



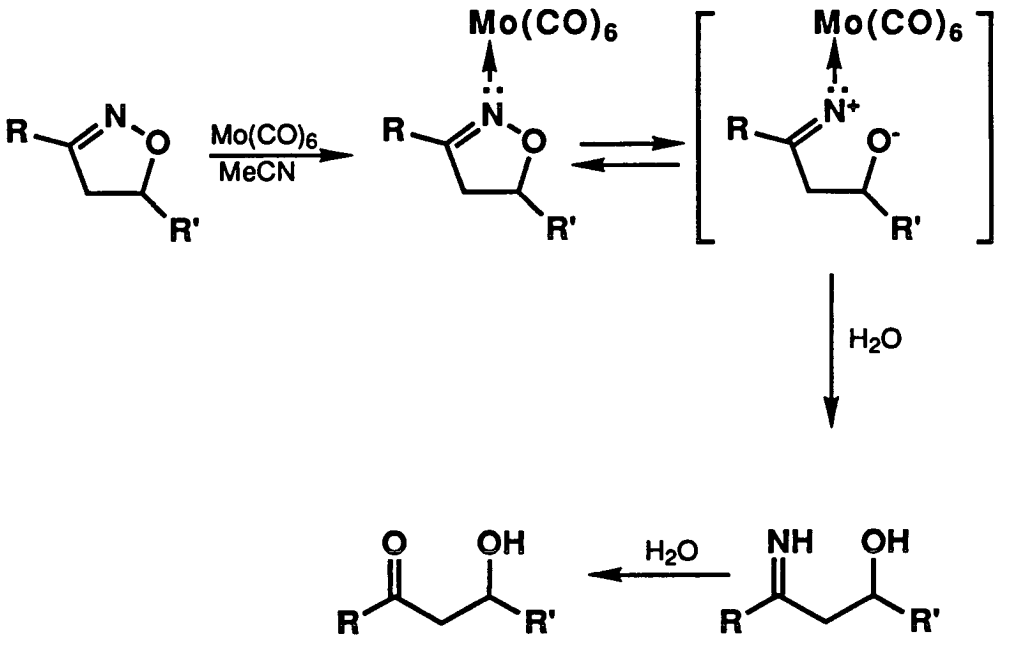
scheme 16

The advantage of boric acid over other reagents is that yields are generally very good, no epimerisation of 4,5-disubstituted isoxazolines is observed, and most acid-sensitive functionality survives exposure to it. However, the limitation of this methodology is that groups sensitive to hydrogenation cannot be present.

Another complementary method for achieving this transformation, based on the conversion of oximes *via* the imine to carbonyl compounds with titanium trichloride,[81] has been developed by Torssell.[28] The reaction is most efficient when carried out at pH 3-4 and so may not be suitable when acid labile groups are present. Another transition metal complex

promoted N-O bond cleavage involves the use of molybdenum hexacarbonyl in wet acetonitrile.[82] This procedure affords the β-

hydroxyketone in good yield, and accommodates a variety of substituents. The proposed mechanism is shown in scheme 17. Treatment of 2-isoxazolines with ozone has also been used to effect this transformation.[79]



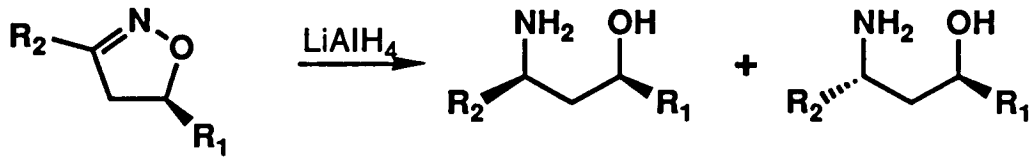
scheme 17

1.5.2 γ-Hydroxyamines

Reduction of 2-isoxazolines to γ-hydroxyamines can be achieved upon treatment with lithium aluminium hydride (LAH) or by catalytic hydrogenation.[26] This conversion, unlike β-hydroxyketone formation, involves a change in the oxidation level of the carbon skeleton, and as a consequence of this a new chiral centre is generated; thus a pair of diastereomeric γ-hydroxyamines results.

Hydrogenation, which initially cleaves the N-O bond and then further

reduces the β-hydroxyimine intermediate, shows poor *erythro/threo* selectivity, typically *ca.* 60:40. In contrast LAH reduces first the C=N bond of the isoxazoline, and the N-O bond of the resulting oxazolidine intermediate is then cleaved.[83 84] Diastereomeric ratios are much higher with LAH (scheme 18).

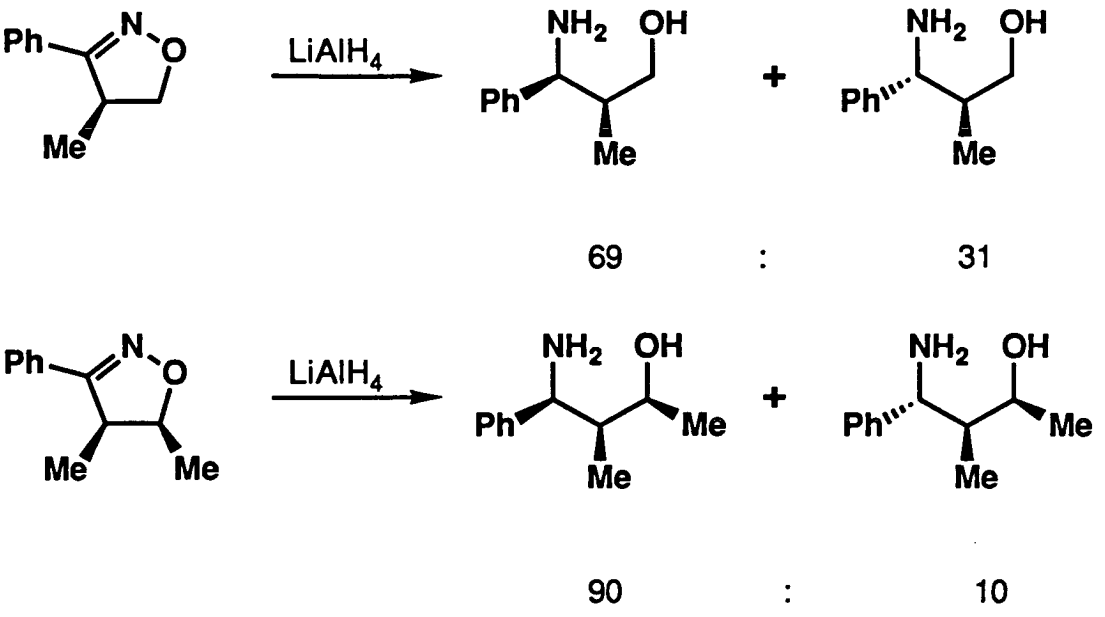


R_1=R_2=Ph	95	:	5
R_1=R_2=Me	85	:	15
R_1=Ph, R_2=Me	95	:	5
R_1=Me, R_2=Ph	87	:	13

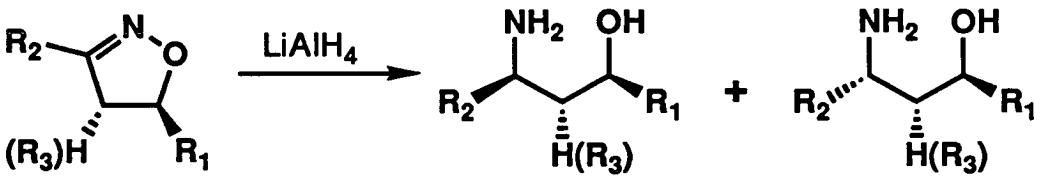
scheme 18

In LAH reductions the hydride is delivered from the sterically least crowded face of the heterocycle; experiments carried out on 3,5- and 3,4-disubstituted isoxazolines show a lower isomer ratio for the latter consistent with lower steric hindrance for the 1,2-arrangement.[85] *Cis*-4,5-disubstituted analogues show an additive effect which results in good diastereoselectivity (scheme 19).

The presence of oxygen containing substituents gives rise to other possible co-ordination sites for the lithium and so may reduce or enhance the selectivity depending on whether it is working with or against the steric effect[86] (scheme 20). Thus, when only alkyl or aryl substituents are involved stereoselectivity is purely a steric phenomenon



scheme 19



$R_1=C_{14}H_{29}$, $R_2=CH_3$	88	:	12
$R_1=C_{14}H_{29}$, $R_2=CH_2OH$	58	:	42
$R_1=C_{14}H_{29}$, $R_2=CH_2OTHP$	78	:	22
$R_1=CH_2OH$, $R_2=CH_3$	37	:	63
$R_1=CH_2OTHP$, $R_2=CH_3$	72	:	28
$R_1=H$, $R_2=Ph$, $R_3=OH$	>90	:	<10

scheme 20

and co-ordination of the lithium and hence delivery of the hydride occurs from the less hindered face of the ring (Fig. 11A). When an oxygen is

present on a substituent, attack from the sterically crowded face can be enhanced due to further lithium co-ordination with the exocyclic oxygen (Fig. 11B).

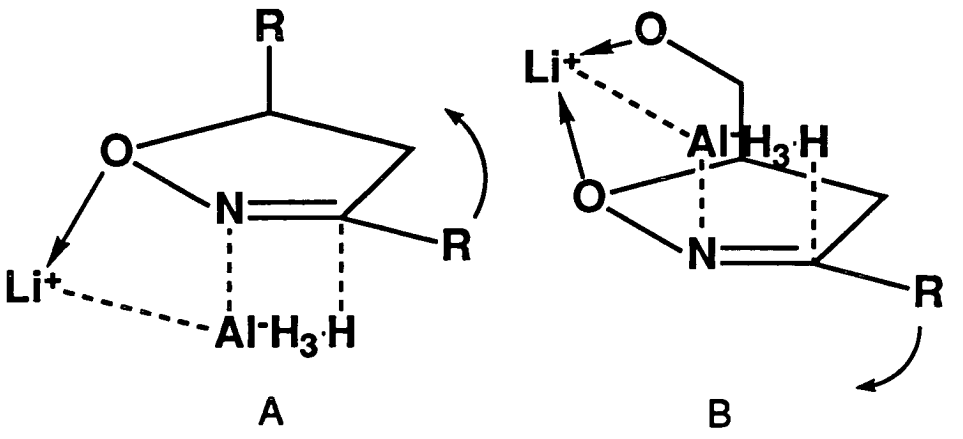
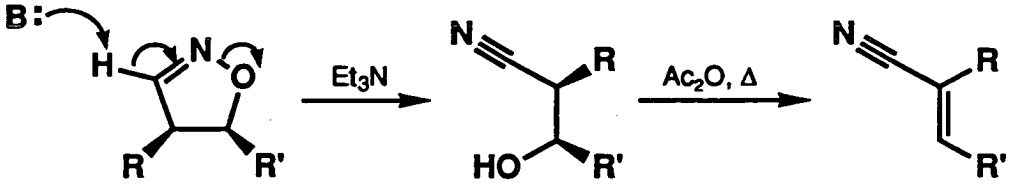


Fig. 11

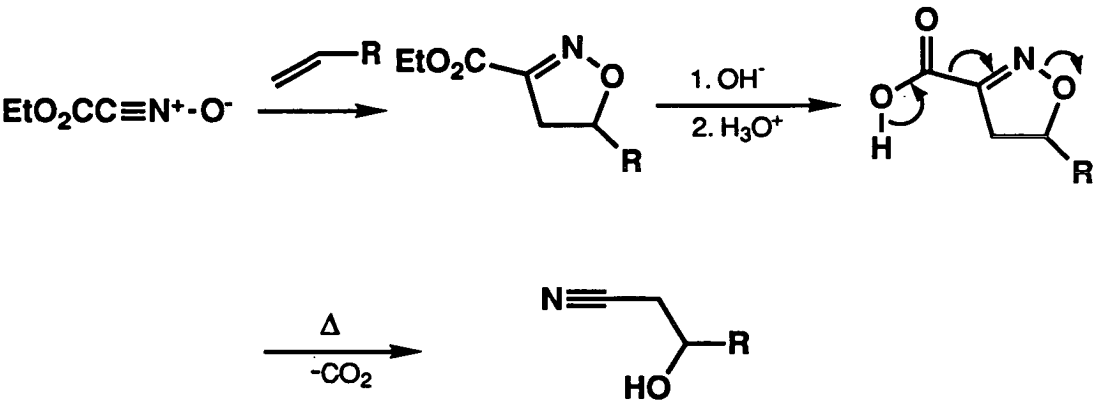
1.5.3 β-Cyanoalcohols and α,β-Unsaturated nitriles

Treatment of 3-unsubstituted-2-isoxazolines with base causes deprotonation and subsequent rearrangement involving N-O bond cleavage to the β-hydroxynitrile[28 87] (scheme 21), which in turn may be converted to the α,β-unsaturated nitrile.



scheme 21

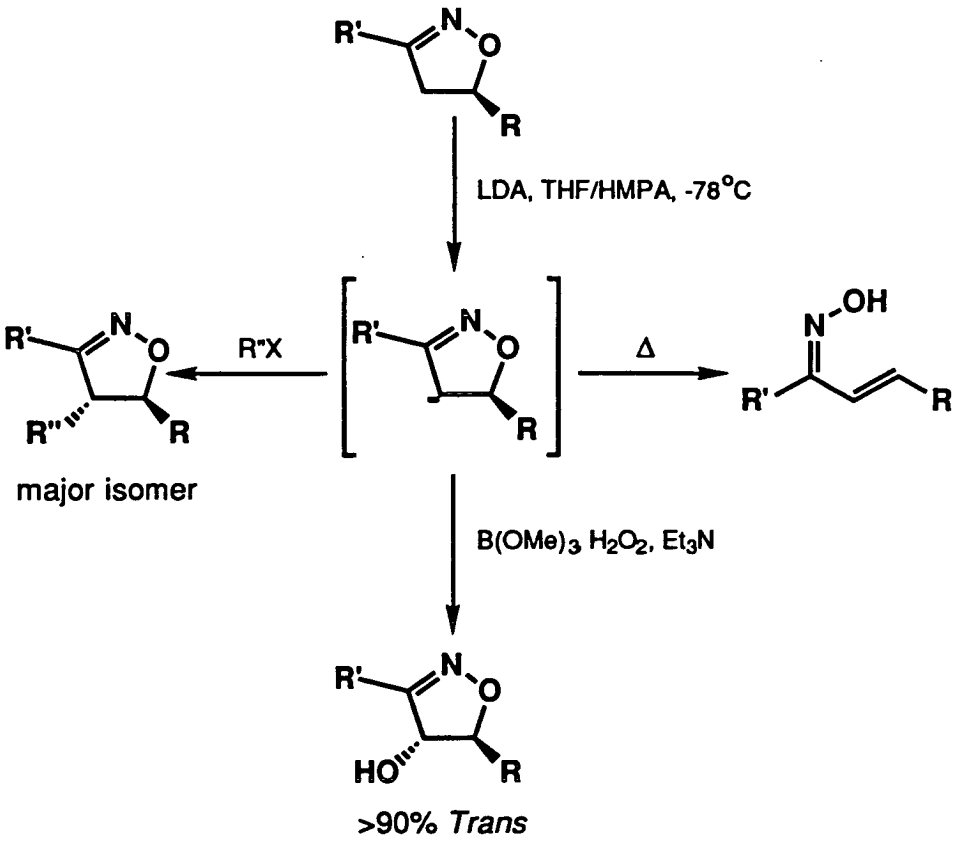
The same conversion has been achieved by thermal decarboxylation of isoxazoline-3-carboxylic acids which are readily available from the cycloaddition reactions of alkenes with ethoxycarbonylformonitrile oxide[88-90] (scheme 22).



scheme 22

1.6. Modification of 2-Isoxazolines *via endo*- and *exo*-Azaenolates

3,5-Disubstituted-2-isoxazolines undergo deprotonation at the 4-position when treated with a strong base such as lithium di-isopropylamide (LDA) at -78°C, to give the *endo*-azaenolate.[91-94] Quenching with an appropriate electrophile affords the 3,4,5-trisubstituted heterocycle with a high degree of stereoselectivity, attack coming from the sterically less hindered face (scheme 23).

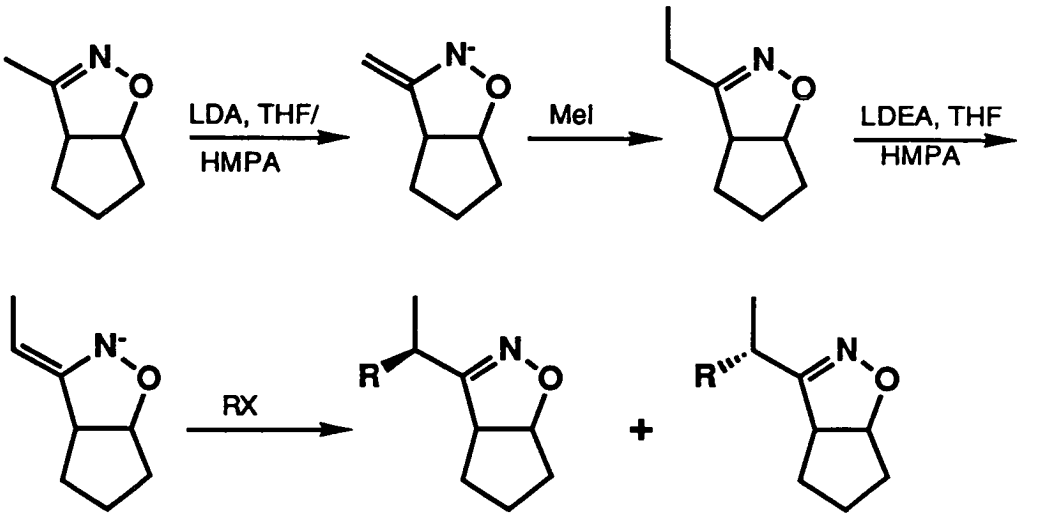


scheme 23

Jager[94] has extended this methodology to include 4-hydroxylation of 2-isoxazolines by treatment of the *endo*-azaenolate with trimethyl borate followed by oxidative work up (H_2O_2 or $^tBuO_2H$). This affords the *trans*-4-hydroxy heterocycle as the major product (>90%) (scheme 23). Allowing the azaenolate solution to warm to room temperature results in the formation of α,β-enoximes[91-93] (scheme 23).

Generation of the *endo*-anion is most efficient when the 3-substituent does not possess an α-hydrogen; when it does, treatment with LDA followed by iodomethane results in a mixture of *endo*- and *exo*-methylated products. Reaction of 3,4,5-trisubstituted-2-isoxazolines possessing an α-methyl or methylene in the 3-position with LDA favours *exo*-azaenolate formation[73 95] (scheme 24), due to slower kinetic

deprotonation of the *endo*-methine.



RX =	CD_3I	85	:	15
	BuI	95	:	5
	$PhCH_2Br$	>96	:	<4

scheme 24

Deprotonation of a 3α-methylene is best achieved by treatment with lithium diethylamide (LDEA). Subsequent alkylation shows a high degree of stereoselectivity caused by diastereofacial selective attack on the *Z*-azaenolate (Fig 12).

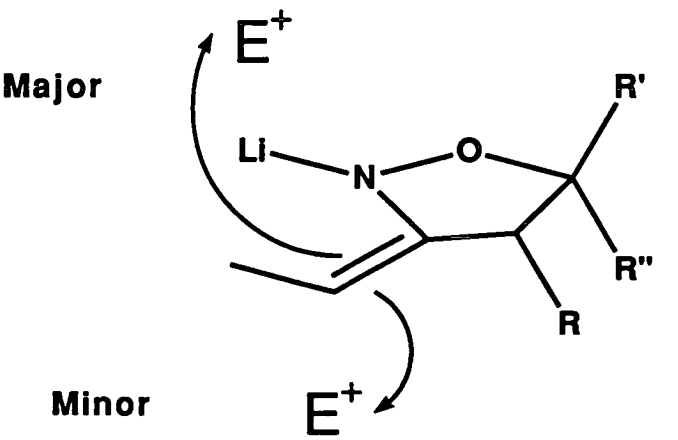


Fig. 12

2. Results and Discussion.

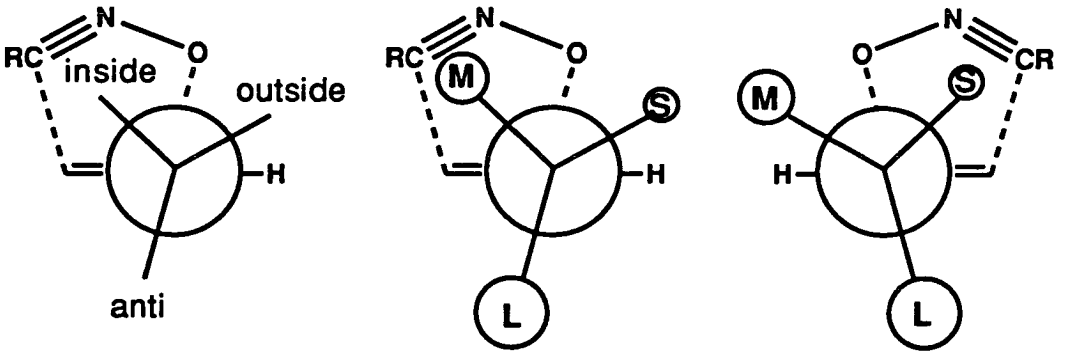
2.1. Cycloaddition Reactions of Nitrile Oxides With Alkenes Bearing an Allylic Nitrogen Substituent at the Asymmetric Centre.

2.1.1. Introduction.

The increased understanding of 1,3-dipolar cycloaddition reactions combined with the development of nitrile oxide/isoxazoline methodology as a convenient stereospecific route to a variety of important acyclic functionality (sect. 1.5) has provided much of the impetus for the investigation of asymmetric induction in the cycloaddition reactions of chiral nitrile oxides and more especially of chiral alkenes.

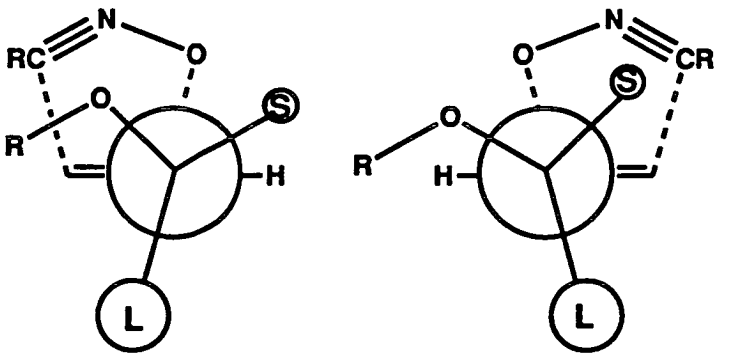
Theoretical investigation of cycloaddition reactions of achiral nitrile oxides with olefins bearing an asymmetric centre at the allylic position,[72] where the substituents at the chiral centre differ only in size, suggests that the major isomer arises *via* a transition state in which the largest group adopts the *anti*-alignment with respect to the forming C-O σ-bond, the medium group is located in the "inside" position and the smallest group is "outside" (Fig 13A). It is predicted that the the minor product is formed through transition state B (Fig. 13) in which the positions of the medium and small groups are exchanged. Selectivity increases as the size difference between the medium and large substituents becomes more pronounced; the small group in the reported examples was hydrogen. Especially good π-facial selectivities have been observed when chiral allyl ethers undergo cycloaddition reactions with nitrile oxides.[71 73] This has been attributed to the preference of the alkoxy substituent to occupy the "inside" position in the transition state giving rise to the *erythro* isomer as the major product (Fig. 14A). This is thought to minimise electron withdrawal from the electron deficient transition state, which would be

maximised if the alkoxy were in the *anti*-alignment *via* overlap of the COσ* orbital with the π-system. The minor *threo* product arises from the transition state in which the alkoxy and the small substituent switch positions (Fig. 14B).



A B

Fig 13



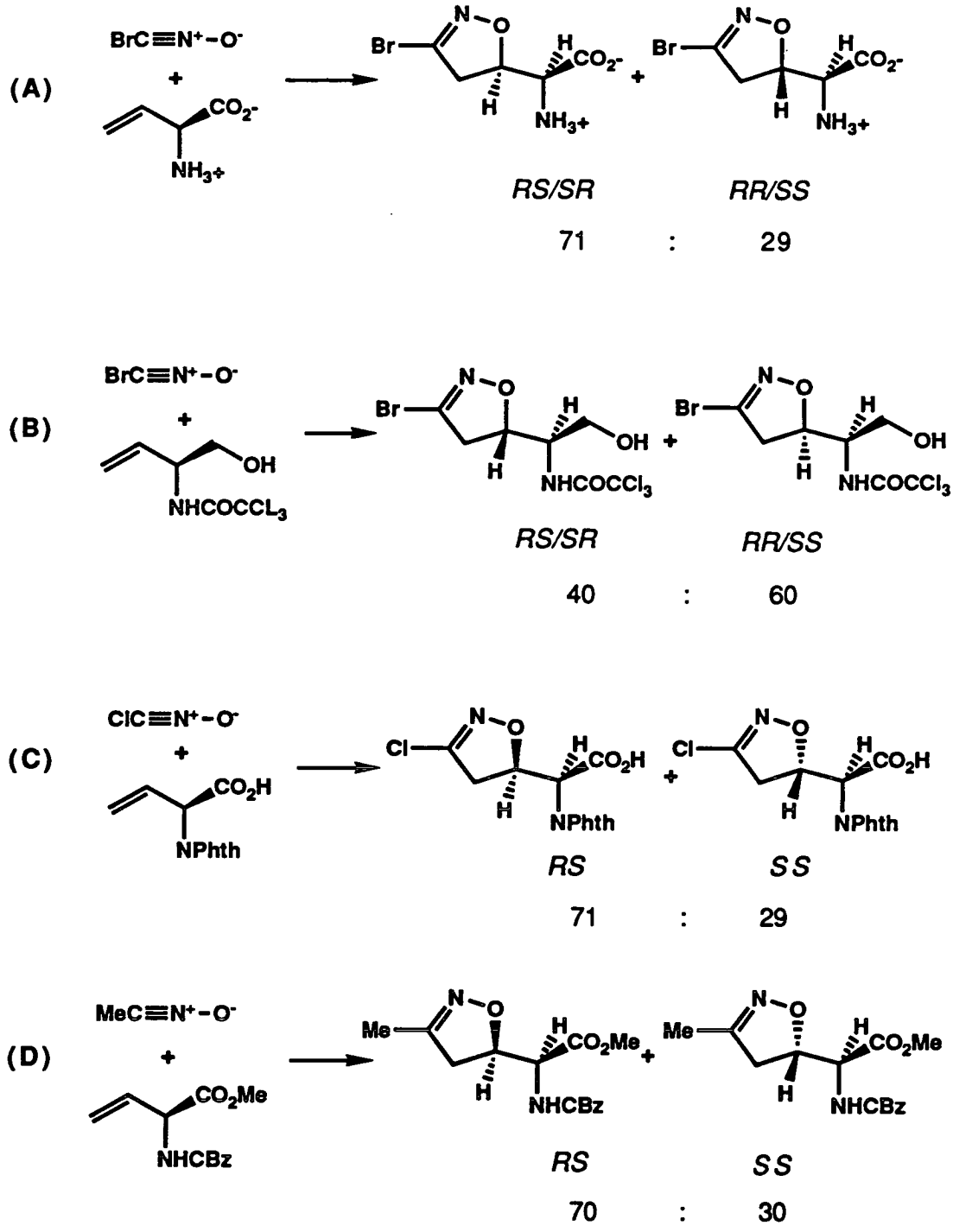
A B

Fig 14

To date there have been a limited number of studies on the effect of an allylic nitrogen.[96-100] The majority of those presented in the literature

involve the cycloaddition of an achiral nitrile oxide with vinylglycine and some protected analogues. In general the π-facial selectivities observed in these reactions are only moderate. Hagedorn and co-workers[98] obtained a cycloadduct ratio of 71:29 in the reaction of bromonitrile oxide with racemic vinylglycine (scheme 25 A), while Vyas *et al*[99] reported a 60:40 mixture of diastereomeric products in the cycloaddition reaction of the same 1,3-dipole with the vinylglycine equivalent 3-trichloroacetamidobut-1-en-4-ol (scheme 25 B). The cycloaddition of chloronitrile oxide, generated by treatment of phosgene oxime with silver nitrate, with *N*-phthalylvinylglycine furnished a 52% yield of cycloadducts as a 71:29 mixture of diastereomers[96 97] (scheme 25 C). Nozoe and co-workers[100] have reported the cycloaddition of acetonitrile oxide with (*S*)-*N*-benzyloxycarbonylaminovinylglycine methyl ester, which afforded a 70:30 mixture of adducts in 53% overall yield (scheme 25 D).

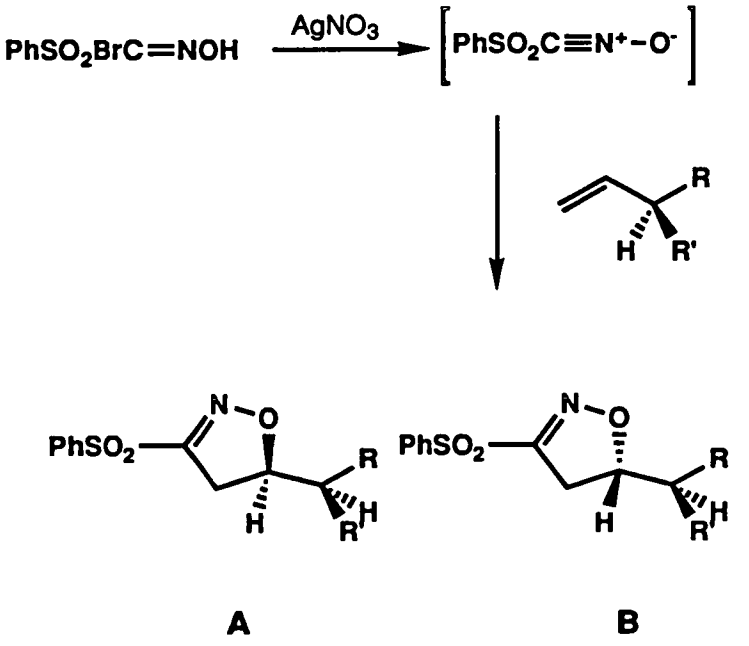
The most extensive study on the effect of an allylic nitrogen on the π-facial selectivity of nitrile oxide cycloaddition reactions was carried out by Wade and co-workers[96]. Benzenesulphonylnitrile oxide was reacted with a wide variety of *N*-protected vinyl glycines and some analogues (Fig. 15). π-Facial selectivities were in general found to be poor (50:50 to 60:40); however, in a few cases useful selectivity was observed, e.g. 70:30, when *t*-butoxycarbonyl- and 3,5-dinitrobenzyloxycarbonyl-nitrogen protection was employed (entries 1 and 4). In all examples in which a carboxylic acid or methylcarboxylate function was present the major product was the 5*R*,α*S* adduct. Wade's results are summarised in Fig. 15.



scheme 25

In the present work three olefins possessing an α-chiral centre bearing a nitrogen substituent, each of which involved a protected or partially protected amino-alcohol, were prepared and the π-facial selectivities of

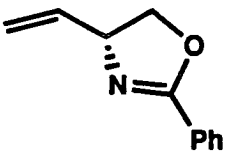
the cycloaddition reactions with some common nitrile oxides investigated.



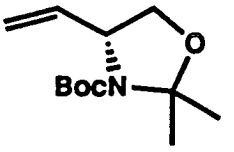
	R	R'	A	:	B
1	CO2H	NHCO2C(Me)3	70	:	30
2	CO2H	NHCO2C(Et)3	60	:	40
3	CO2H	NHCO2CH2(9-anthryl)	60	:	40
4	CO2H	NHCO2CH2-[3,5-$(NO2)_2$C6H3]	70	:	30
5	CO_2H	NHCO[3,5-$(NO_2)_2C_6H_3$]	60	:	40
6	CO_2H	NHCOMe	62	:	38
7	CO_2H	N-[2-(NO_2)Phth	60	:	40
8	CO_2H	NPhth	62	:	38
9	CO_2H	NHCbz	55	:	45
10	CO_2Me	NHCbz	55	:	45
11	CO_2Me	NPhth	60	:	40
12	CH_2OH	NHCbz	47	:	53
13	CH_2OAc	NHCbz	50	:	50
14	$CMe)_2OH$	NHCbz	34	:	66

Fig 15

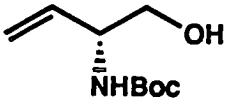
The two fully protected α-amino-alcohols were in the form of five membered heterocyclic rings: an oxazoline (**11**) (4,5-dihydro-oxazole) and an *N*-Boc-protected oxazolidine (**12**). The former is believed to be the first example of a dipolarophile bearing an allylic sp^2-hybridised nitrogen at an α-chiral centre. The partially protected amino-alcohol, (2*R*)-2*N*-*t*-butoxycarbonylaminobut-3-en-1-ol (**13**), was derived by partial deprotection of the oxazolidine (**12**).



(11)



(12)



(13)

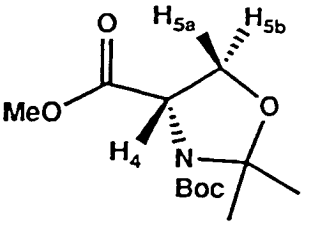
2.1.2. Synthesis of (4*R*)-3-(*N*-*t*-butoxycarbonyl)-2,2-dimethyl-4-vinyloxazolidine (12) and (4*R*)-2-(*N*-*t*-butoxycarbonyl-amino)but-3-en-1-ol (13).

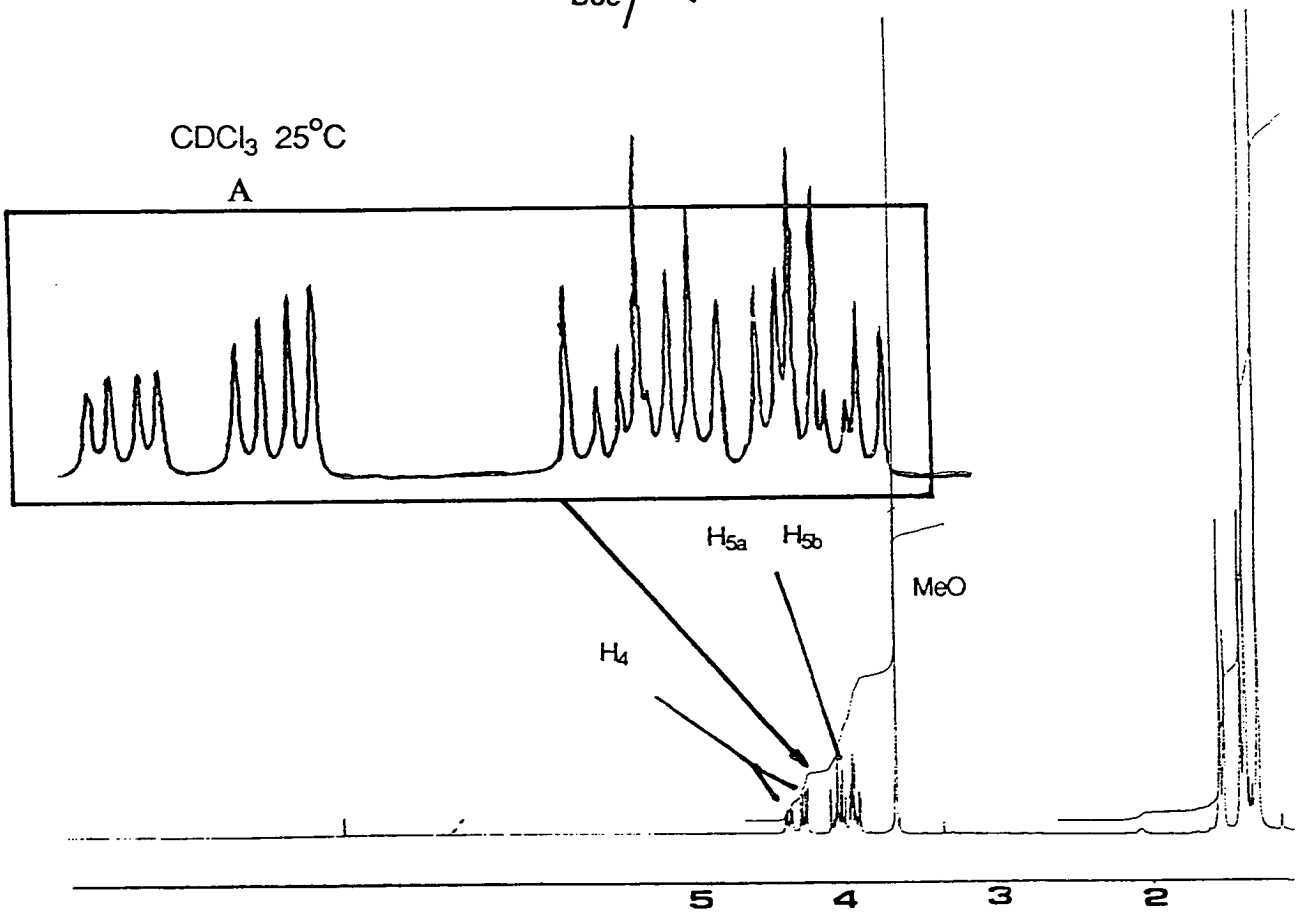
The title olefin **(12)** was prepared in five steps from the readily available amino acid (*S*)-serine **(14)** according to the sequence shown in scheme 26. The key intermediate, aldehyde **(18)**, has been shown by Garner and Park[101] to retain the enantiomeric purity of the starting amino acid. In the literature synthesis (*S*)-serine **(14)** was converted first to the *N*-Boc protected amino acid (Boc_2O, pH >10) followed by treatment of the crude product with diazomethane, which afforded (*S*)-serine-*N*-Boc-methyl ester **(16)** in an overall yield of 80-90%.

In the present work, to avoid the need to use diazomethane, (*S*)-serine was first converted to the methyl ester hydrochloride (82%) by treatment with methanol and thionyl chloride. Reaction of the ester with di-*t*-butyldicarbonate (Boc_2O) in pyridine afforded the *N*-Boc derivative as a viscous oil (98%), which was converted to the oxazolidine methyl ester **(17)** in 78% yield according to the literature procedure[101] (DMP, TsOH, C_6H_6) (scheme 26).

The ^{1}H-NMR spectrum of **(17)**, consistent with the observations of Garner and Park,[101] showed two sets of signals at room temperature (Fig 16A) indicating the existence of a dynamic equilibium between two conformations of the oxazolidine ring. These workers found that running the spectrum at 75°C in C_6D_6 caused the signals to coalesce. However, in our hands heating the probe to 75°C and using the same solvent gave rise to broad singlets rather than a fully resolved spectrum (Fig 16B).

The ^{13}C-NMR spectrum at the two temperatures shows an identical effect. At ambient temperature several of the signals are doubled, whereas heating the sample to 80°C brings about coalescence of those


O
H_{5a}
H_{5b}
MeO
O
H_4
N
Boc


$CDCl_3$ 25°C
A
H_{5a}
H_{5b}
MeO
H_4
5
4
3
2

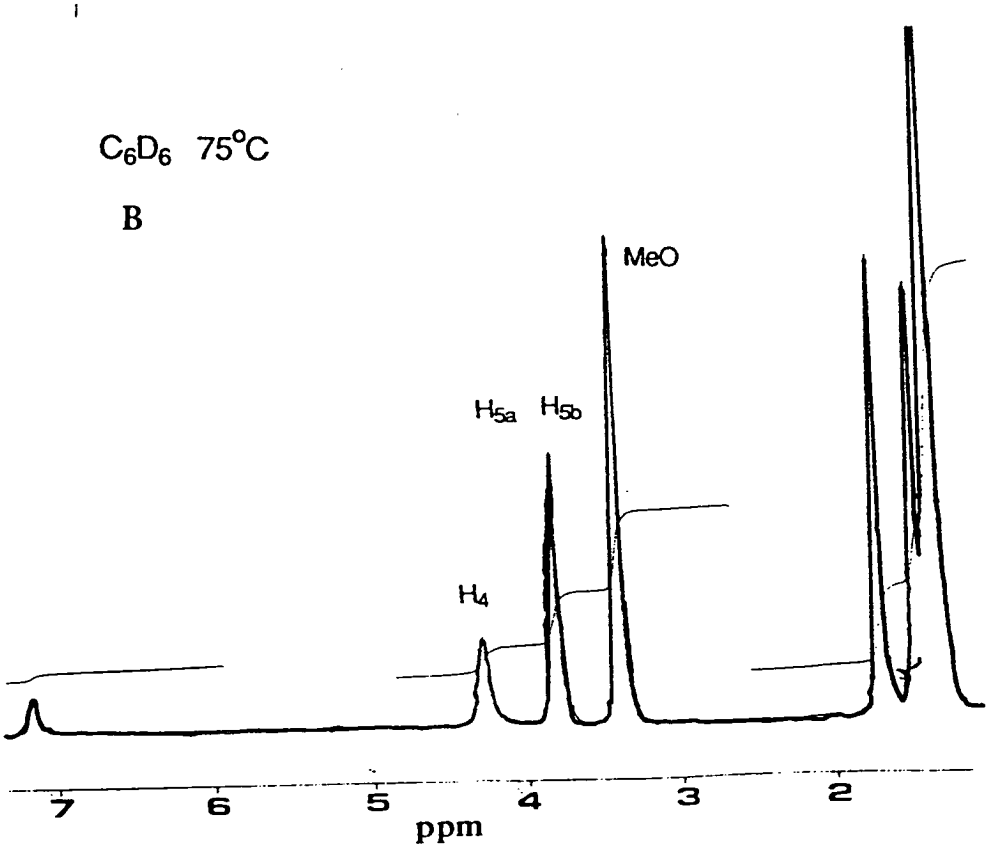
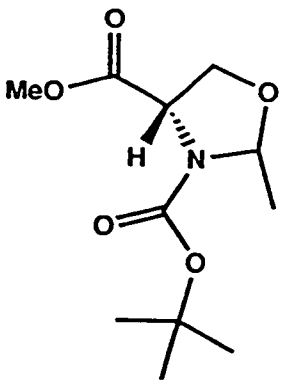
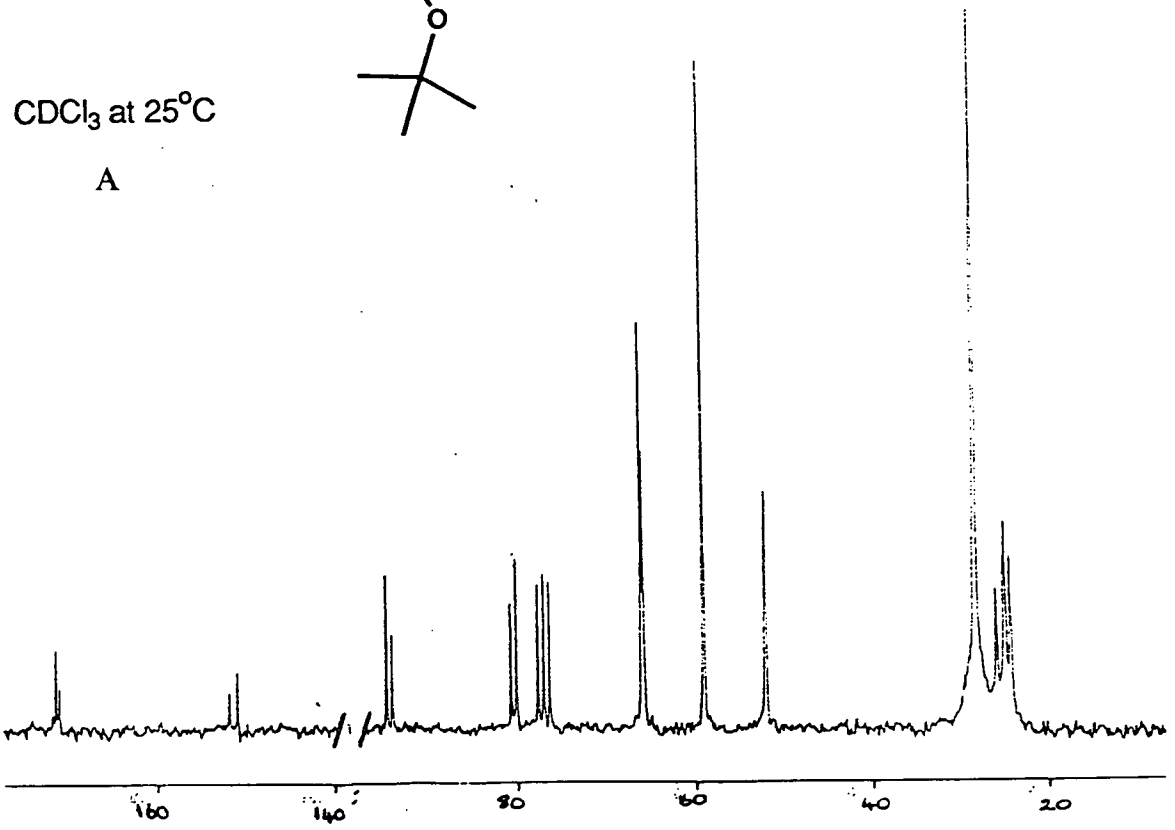

C_6D_6 75°C
B
MeO
H_{5a}
H_{5b}
H_4
7
6
5
4
3
2
ppm

Fig. 16



$CDCl_3$ at 25°C

A



C_6D_6 at 80°C

B

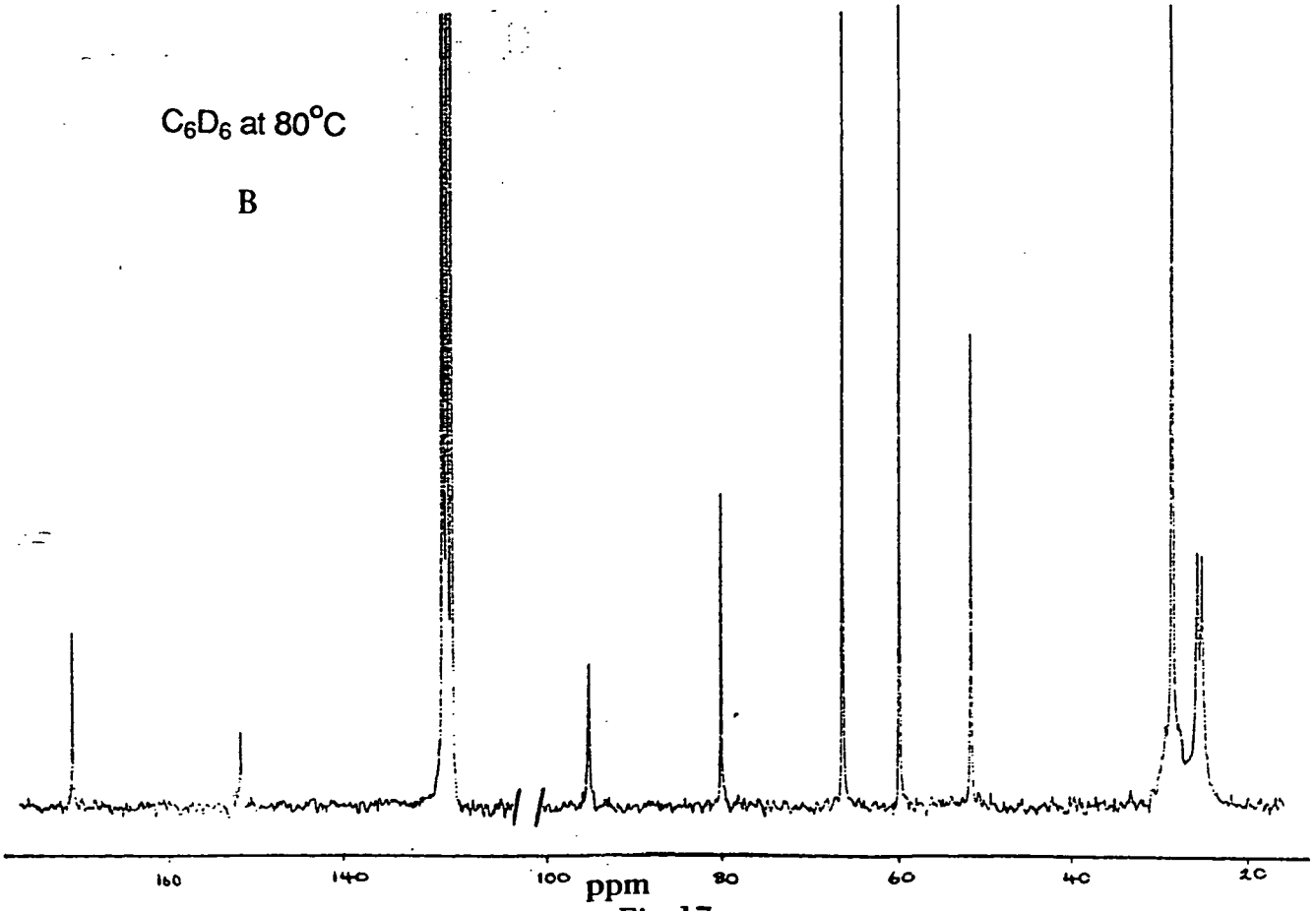
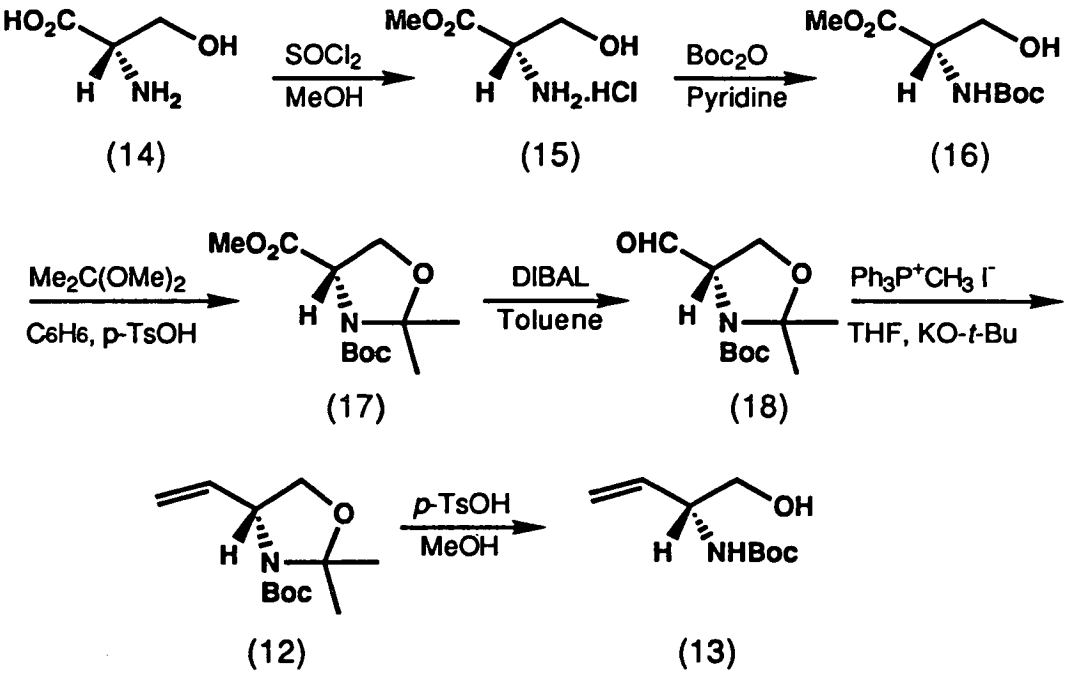


Fig.17

peaks (Fig 17A and B).



scheme 26

The methyl ester oxazolidine **(17)** was converted to the aldehyde **(18)** by reduction with DIBAL in 88% yield. Although the ^{1}H-NMR spectrum of **(18)** after distillation showed it to be slightly impure, it was used in subsequent reactions without further purification because both of the compounds derived from it, the oxime **(40)** and the olefin **(12)**, were more easily separated from the impurities by flash column chromatography than was the aldehyde.

Reaction of **(18)** with the ylide generated from methyltriphenyl-phosphonium iodide, on treatment with potassium-*t*-butoxide, furnished the desired alkene **(12)** in 66% yield as a clear oil after chromatography. This vinyl oxazolidine **(12)** which had previously been prepared by

Moriwake and co-workers[102] from the same aldehyde, was reported to undergo complete racemisation under the basic conditions of the Wittig reaction (Ph_3PMeBr, KH, C_6H_6). To avoid this problem they used non-basic olefination methodology ($AlMe_3$, Zn, CH_2I_2) and isolated the optically pure alkene in 75% yield $[\alpha]_D$ (28°C) +15° (c2.5 in $CHCl_3$). However, in the present work the conditions employed in the Wittig reaction (Ph_3PMeI, THF, KO-*t*-Bu) do not appear to have caused any racemisation of the vinyl oxazolidine, which shows identical optical rotation to that reported by Moriwake.[102] The reasons for the loss of stereochemical purity in the literature example and the retention of chiral integrity in the present case are difficult to explain since Moriwake did not publish the procedure for the Wittig reaction. However, in our olefination protocol no excess of potassium-*t*-butoxide was used (with respect to the phosphonium salt) and generous times were allowed for ylide formation (2 hours) before adding the aldehyde; thus the ylide would be the strongest base to which the aldehyde and alkene were exposed.

Treatment of vinyl oxazolidine **(12)** with *p*-toluenesulphonic acid in methanol[102] furnished (4*R*)-2-(*N*-*t*-butoxycarbonylamino)but-3-en-1-ol **(13)** in 76% yield with $[\alpha]_D$ (20°C) +26.3° (c 1.48 in $CHCl_3$), [(lit.,[102] $[\alpha]_D$ (26°C) +29° (c 2.1, $CHCl_3$)]. This provided further evidence for the non-racemisation of the vinyl oxazolidine **(12)** during the Wittig reaction. The availability of acyclic olefin **(13)** allows a comparison to be made between the π-facial selectivity in nitrile oxide cycloadditions with the cyclic vinyl oxazolidine **(12)**, in which the alcohol moiety of the masked amino alcohol is protected and the acyclic olefin **(13)** in which the hydroxyl function is exposed.

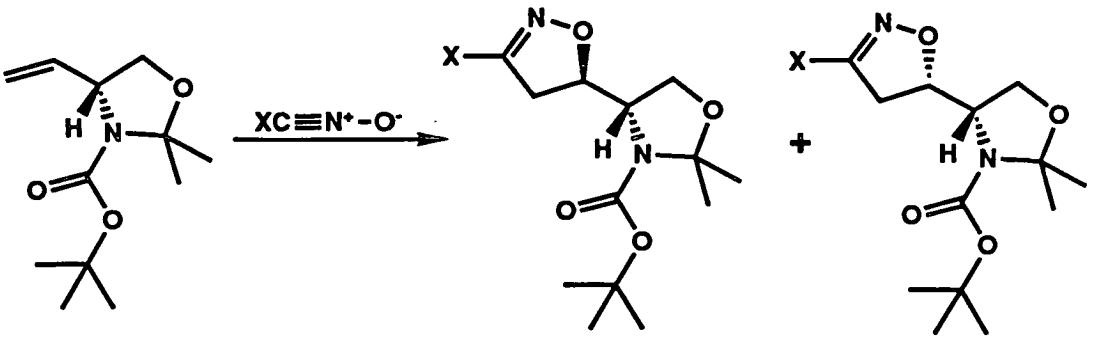
2.1.3. Cycloaddition Reactions of Nitrile Oxides with (4*R*)-3-(*N*-*t*-butoxycarbonyl)-2,2-dimethyl-4-vinyloxazolidine (12)

The title alkene was used in cycloaddition reactions with benzonitrile oxide, ethoxycarbonylformonitrile oxide and bromonitrile oxide. The first two were generated *in situ* by treatment of the corresponding hydroximoyl chlorides with triethylamine. Bromonitrile oxide was generated *in situ* by reaction of dibromoformaldoxime with triethylamine. It is worthy of note that bromonitrile oxide is usually generated using a two phase system with aqueous sodium[98 99] or potassium[103] bicarbonate as the base. Torssell[103] has claimed that triethylamine is not a suitable base for this nitrile oxide due to the possibility that it will react with the 1,3-dipole. However, in this work triethylamine has been used to form bromonitrile oxide without any discernible problems.

All of these cycloaddition reactions were carried out at room temperature in diethyl ether and triethylamine in the same solvent was added over approximately 24 hours by means of a motorised syringe pump. Excess of the nitrile oxide precursors were used in all cases to ensure complete consumption of the olefin. The cycloadducts were isolated in good yield (scheme 27) as inseparable mixtures of diastereomers, which were easily isolated from other reaction products by flash column chromatography. The diastereomeric ratios (scheme 27) were determined from the integrals of the isoxazoline H_5 signals in the ^{1}H-NMR spectra of the adduct mixture (Fig 18). The π-facial selectivity of these reactions was low (*ca.* 2:1) with the *erythro* (5*R*,4'*S*) isomer being favoured. The assignment of absolute stereochemistry is discussed latter in this section.

This result is consistent with previous literature reports for nitrile oxide cycloadditions with chiral allyl ethers, which show that the *erythro* adduct

is the favoured product.[71 73]



(12)

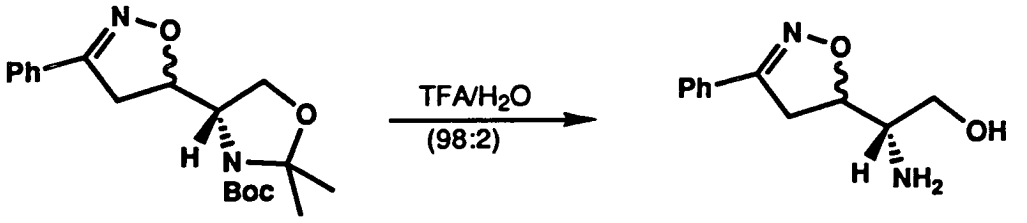
5*R*, 4'*S*
Erythro

5*S*, 4'*S*
Threo

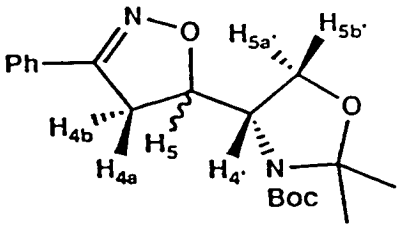
X	Yield (%)			Ratio	
Ph	85	(19a)	66	(19b)	34
EtO_2C	89	(20a)	68	(20b)	32
Br	87	(21a)	65	(21b)	35

scheme 27

In an attempt to separate the diastereomeric products resulting from the reaction with benzonitrile oxide the mixture of **(19a)** and **(19b)** was treated with trifluoroacetic acid and water (98:2),[104] which resulted in complete deprotection of the β-amino-alcohol functionality in 76% yield (scheme 28). The resulting mixture of diastereomeric amino-alcohols was again not amenable to chromatographic separation.



scheme 28


N
O
Ph
H5a'
H5b'
O
H4b
H5
H4a
H4'
N
Boc

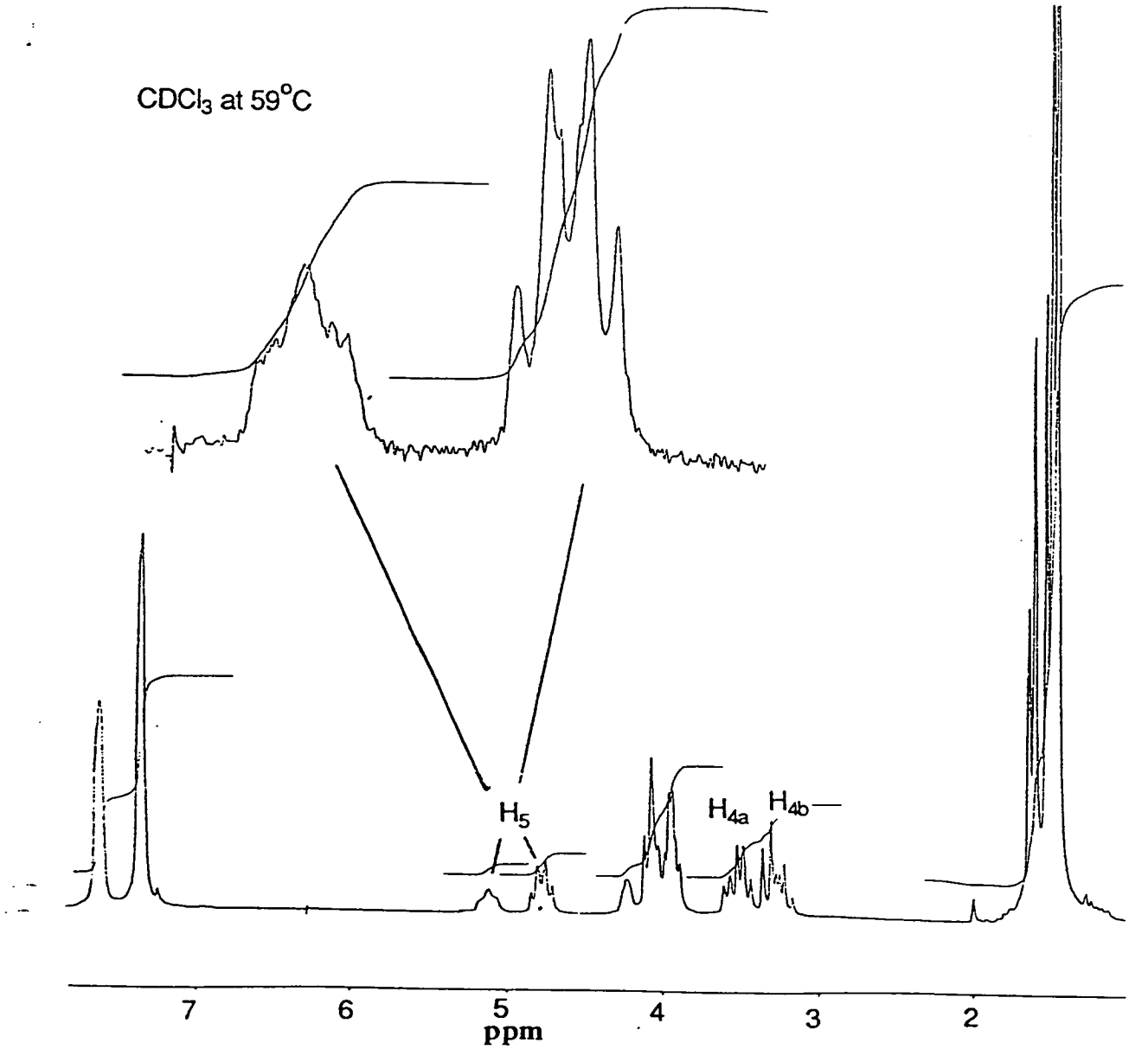
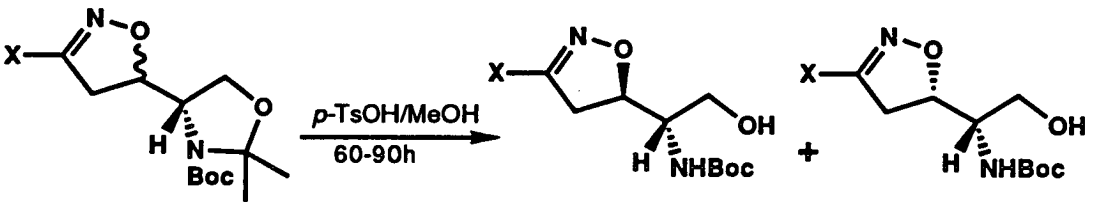

CDCl3 at 59°C
H5
H4a
H4b
7
6
5
4
3
2
ppm

Fig. 18

In the preparation of (4*R*)-2-(*N*-*t*-butoxycarbonylamino)but-3-en-1-ol (**13**) from the vinyl oxazolidine (**12**) (scheme 26) a catalytic amount of *p*-toluenesulphonic acid in methanol was used to promote deacetonisation while leaving the *N*-Boc protection intact. This procedure was applied to each of the mixtures of cycloadducts and resulted in clean exposure of the *N*-Boc-amino-alcohol moiety (scheme 29). Extended reaction times were required for this conversion (60-90 h) and in all cases appreciable amounts of starting materials were recovered, which were easily separated from the products by flash column chromatography. The diastereomeric products were separated from each other by further chromatography. In all cases the *erythro* product showed lowest polarity on silica (hexane/EtOAc). Isolation of the isomeric products from this partial deprotection protocol allowed isolated ratios of products to be obtained. These were in excellent agreement with the values derived from the ^{1}H-NMR spectra of the cycloadduct mixtures (scheme 27).



5*R*, 2'*S*
Erythro

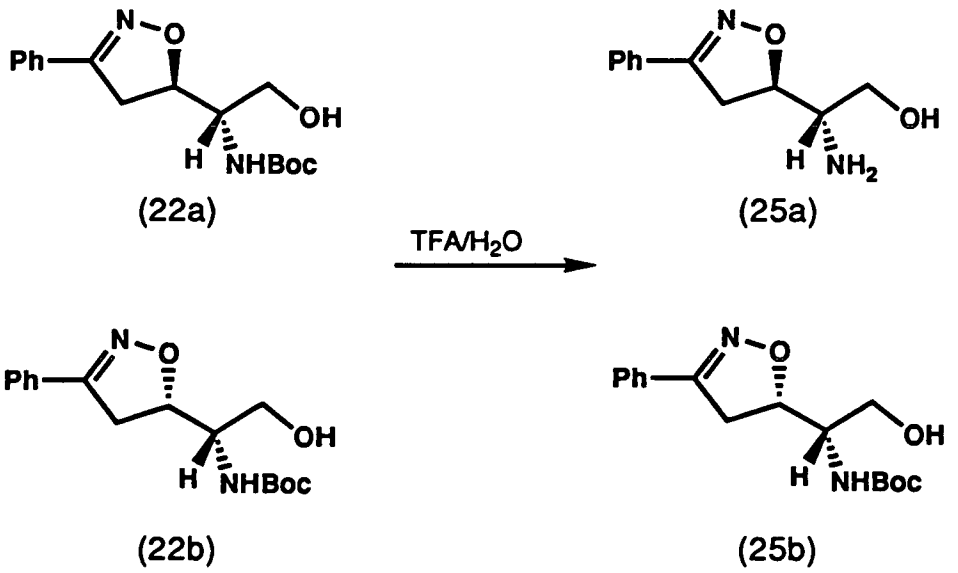
5*S*, 2'*S*
Threo

X		Yield (%)[1]	Ratio[2]	
Ph	(19a & b)	70 (80)	(22a) 64 (66)	(22b) 36 (34)
EtO_2C	(20a & b)	67 (84)	(23a) 67 (68)	(23b) 33 (32)
Br	(21a & b)	63 (76)	(24a) 66 (65)	(24b) 34 (35)

1. Yields in brackets are based on recovered starting materials.
2. Figures in brackets are the ^{1}H-NMR ratios for the cycloadducts.

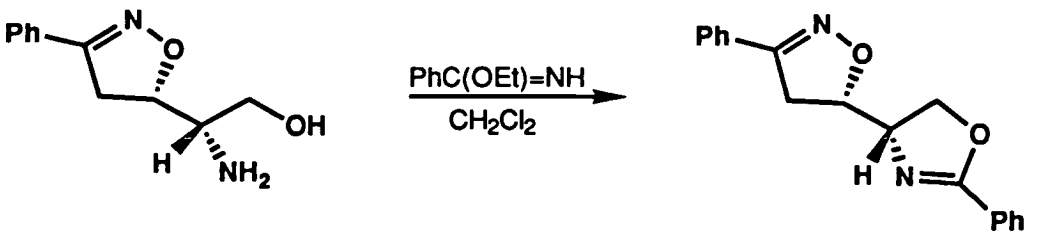
scheme 29

The successful separation of all of the diastereomeric pairs at once made possible the assignment of the absolute stereochemistry of the cycloaddition products. Attempts to grow crystals of (5*R*,2'*S*)-2'-(*N*-*t*-butoxycarbonylamino)-2'-(3-phenyl-2-isoxazolin-5-yl)ethanol **(22a)** and the (5*S*,2'*S*) isomer **(22b)** for *X*-ray analysis proved unsuccessful; removal of the *N*-Boc protection (TFA/H_2O) furnished both of the completely deprotected β-amino-alcohols **(25a)** and **(25b)** (scheme 30) in reasonable yields. Again, attempts to obtain crystals suitable for *X*-ray analysis proved fruitless.



scheme 30

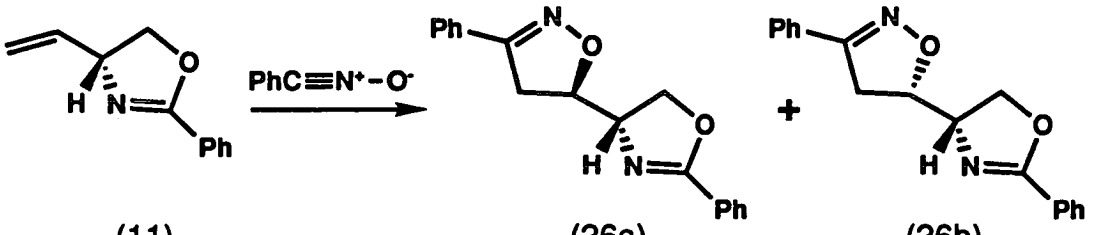
However, reaction of aminoalcohol **(25b)**, derived from the minor isomer in the cycloaddition reaction, with ethyl benzimidate (scheme 31) afforded, in 27% yield after preparative tlc, (5*S*,4'*S*)-3-phenyl-5-(2-phenyl-4,5-dihydro-oxazol-4-yl)-2-isoxazoline **(26b)**, which was identical with the minor product formed in the cycloaddition reaction between benzonitrile oxide and 2-phenyl-4-vinyl-4,5-dihydro-oxazole **(11)** (scheme 32) (see also section 2.1.8).



(25b) (26b)

scheme 31

The absolute stereochemistry of **(26b)** had been assigned on the basis of an *X*-ray structure of the major cycloadduct **(26a)** which showed it to be the *erythro* (*RS/SR*) isomer. The major product in the cycloaddition of benzonitrile oxide with the vinyl oxazolidine **(12)** is therefore the (5*R*,4'*S*) isomer while the minor product has the (5*S* 4'*S*) configuration. The stereochemistry of the adducts of ethoxycarbonylformonitrile oxide and bromonitrile oxide were assigned on the basis of this observation.



(11) (26a) (26b)

only one enantiomer of each compound is shown

scheme 32

2.1.4. Explanation for the Observed π-Facial Selectivities.

By analogy with the work of Houk and Jager[71] on chiral allylic ethers there are six possible transition states for the formation of the products in these cycloaddition reactions (Fig 19). However, while these Felkin-type transition states can be drawn for the arrangement of the substituents at the asymmetric centre with respect to the forming C-O bond of the isoxazoline ring, the overall picture is likely to be more complicated for 4-vinyloxazolidines due to the possibility of other conformational forms existing within the flexible heterocyclic ring.

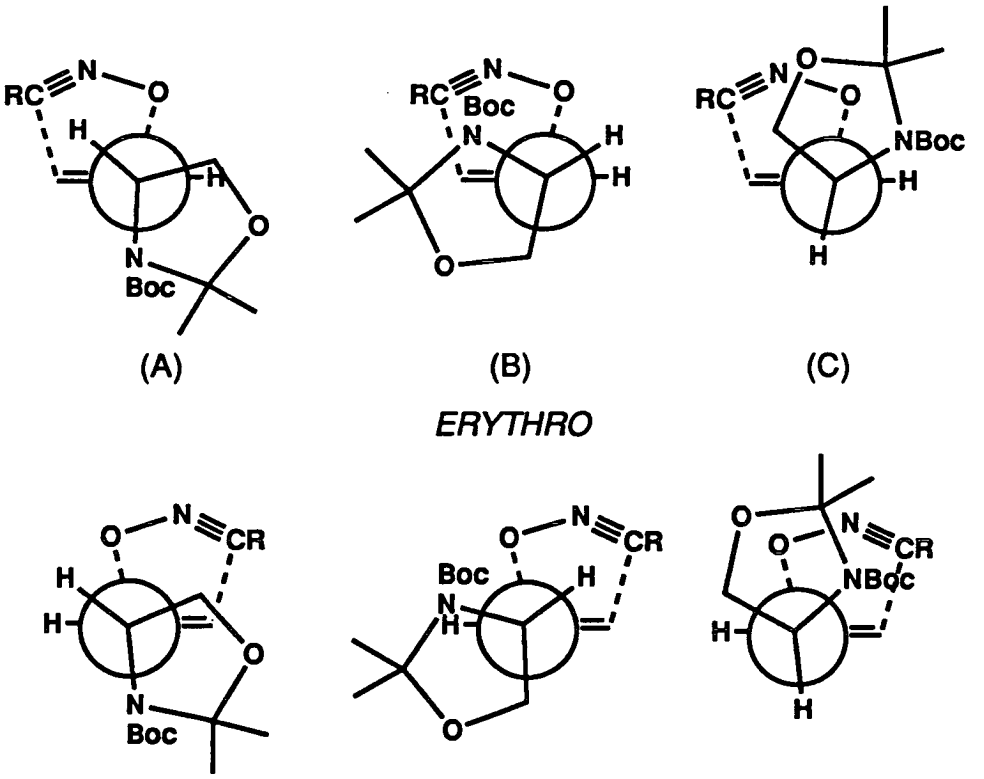


Fig 19

Wade and co-workers,[96] in their extensive study of π-facial selectivity in the 1,3-dipolar cycloaddition reactions of benzenesulphonylcarbonitrile oxide with a variety of *N*-protected vinyl-amino acids and alcohols (Fig. 15), found no strong evidence for any stereoelectronic effect induced by the allylic nitrogen. However, they did state that the allylic nitrogen showed a preference to be near to the carbon-carbon double bond (the "inside" position) (Fig. 20) and that the nitrile oxide did not attack *anti* to the nitrogen substituent. On the other hand Mann and co-workers[105] have proposed a Felkin-Anh model for the 1,4-addition of lithium dialkyl cuprates to the oxazolidine Michael acceptor (Fig. 21) in which the nitrogen adopts the *anti*-alignment with respect to the incoming nucleophile.

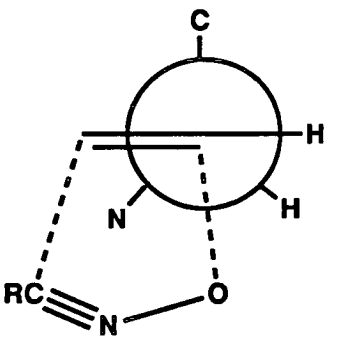


Fig 20

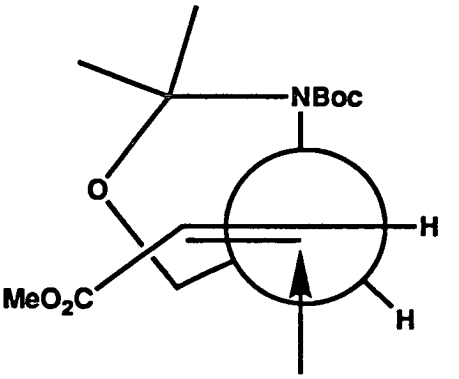


Fig 21

The observed isomer ratios for the cycloaddition reactions with the vinyl oxazolidine **(12)** indicate that the nitrogen does not preferentially adopt the *anti*-arrangement (Fig. 19 , A and D). Examination of these transition states shows that in **A** the bulkier $-CH_2O-$ is in the sterically more demanding "outside" position, whereas in **D** it adopts the less crowded "inside" position. Thus if the steric bulk of the *N*-Boc group is so great as to force it to take up the sterically least demanding *anti*-position, the

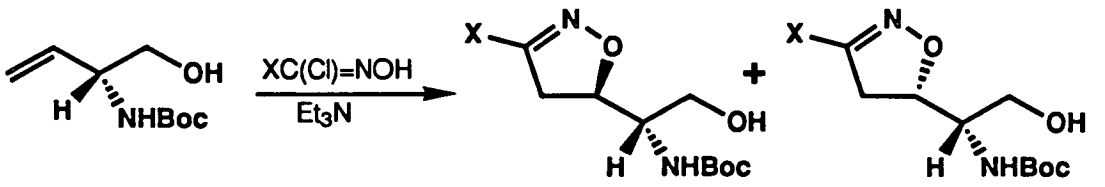
threo (*S*,*S*) cycloadduct arising from transition state **D** would be expected to be the major reaction product, but this is not the case.

The transition states which place hydrogen in the *anti*-alignment **C** and **F** would, if they were the two favoured ones leading to the *erythro* and *threo* products respectively, again be expected to result in the *threo* (*S*,*S*) adduct being the major product. This is because the large *N*-Boc group is in the sterically more demanding "outside" position in transition state **C** which results in the formation of the *erythro*-isomer. However, if the prediction of Wade[96] that there is little evidence for a stereoelectronic contribution to the energetics of the transition state is extrapolated to this system, then the assignment of the energy maxima in this pathway would have to be based purely on steric considerations. It is therefore reasonable to ignore the transition states **C** and **F** which place hydrogen, the smallest substituent, in the *anti*-position of a Felkin transition state.[106] On the basis of the preceding arguments it is predicted that the major *erythro* (*R*,*S*) adduct results from transition state **B**, which locates the nitrogen substituent in the "inside" position and the -CH_2O- moiety *anti*. The minor *threo* (*S*,*S*) product can be considered to arise from either transition states **D** or **E**.

2.1.5. Nitrile Oxide Cycloaddition Reactions of (2*R*)-2-(*N*-*t*-butoxycarbonylamino)but-3-en-1-ol (13).

1,3-Dipolar cycloaddition reactions with benzonitrile oxide and ethoxycarbonylformonitrile oxide were carried out with the title alkene (**13**). These reactions allow some comparison to be made between the π-facial selectivities when the α-hydroxy function is masked in the

oxazolidine ring and exposed in the acyclic *N*-Boc-amino-alcohol form. For the latter olefin there is the possibility of hydrogen bonding between the alcoholic moiety and the nitrile oxide oxygen in the transition state.[71] The results of these cycloaddition reactions are shown in scheme 33.



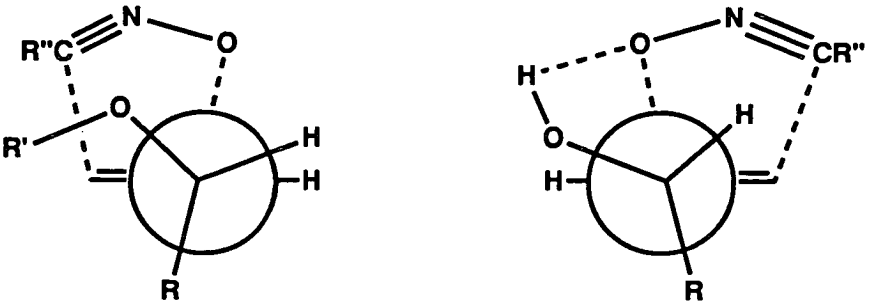
(13)

X	Yield (%)		Ratio 5*R*, 2'*S*		5*S*, 2'*S*
Ph	71	(22a)	40	(22b)	60
EtO_2C	64	(23a)	46	(23b)	54

scheme 33

The diastereomeric ratios in these experiments were obtained by isolation of the products using flash column chromatography. The effects of exposing the hydroxy function in these cycloaddition reactions are three-fold: the combined yields of the cycloadducts are lower; the π-facial selectivitity is reduced; and the *threo* (*S*,*S*) isomer is the major product of the reaction. The reduction and reversal of π-facial selectivity is not without literature precedent. Houk and Jager[71] reported that nitrile oxides undergo cycloaddition reactions with chiral allylic ethers affording, as the major product, the *erythro* isomer *via* the transition state that locates the ethereal oxygen in the "inside" position (Fig 22A). The corresponding alcohols were found to be less selective and favoured, to a slight extent, the *threo* adduct. The configuration of the major product was attributed to

a transition state in which the alcoholic moiety adopts the "outside" position allowing a slightly more favourable hydrogen bonding interaction with the nitrile oxide oxygen (Fig 22B).



(A) (B)

Fig 22

In the present work the reversal of π-facial selectivity can be attributed to a hydrogen bonding interaction between the hydroxyl function of (2*R*)-2-(*N*-*t*-butoxycarbonylamino)but-3-en-1-ol **(13)** and the oxygen of the 1,3-dipole. However, **(13)** is a homoallylic alcohol as opposed to the allylic alcohols of Houk and Jager, and location of the hydroxy function in the "outside" position would result in the formation of the *erythro* adduct. Consideration of the transition states which place the alcoholic function in both the "inside" and "outside" positions suggests that in both arrangements hydrogen bonding would involve a six membered ring, either a pseudo-boat or a chair conformation. Presumably the transition state which places the alcohol function in the "inside" position is favoured, resulting in the slight bias towards the *threo* product (Fig. 23). The other possible hydrogen bonding interaction, with the NHBoc group, does not appear, from examination of models, to be very favourable.

The arguments presented here require that the *N*-Boc-amino function is located in the *anti*-position in both transition states. This is contrary to the

proposal of Wade *et al*[96] who stated that the nitrile oxide oxygen does not attack *anti* to the nitrogen function. These workers carried out the cycloaddition reaction of benzenesulphonylcarbonitrile oxide with a very similar olefin, only differing in the amine protection, with CBZ replacing Boc.

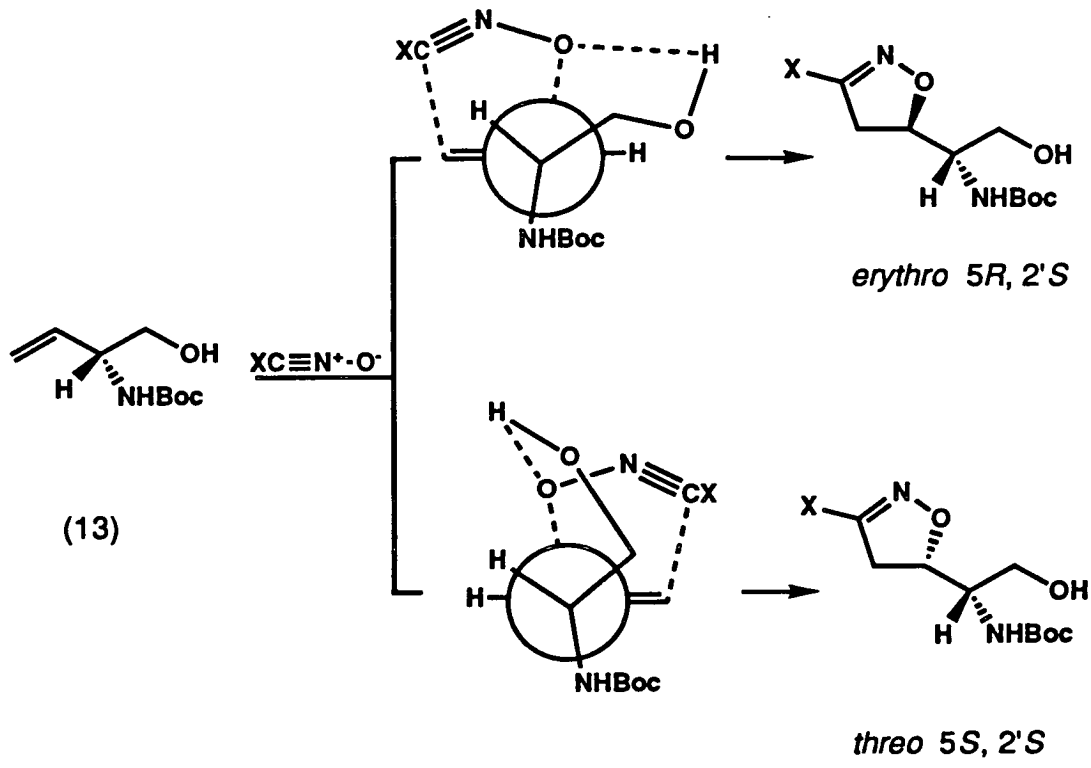
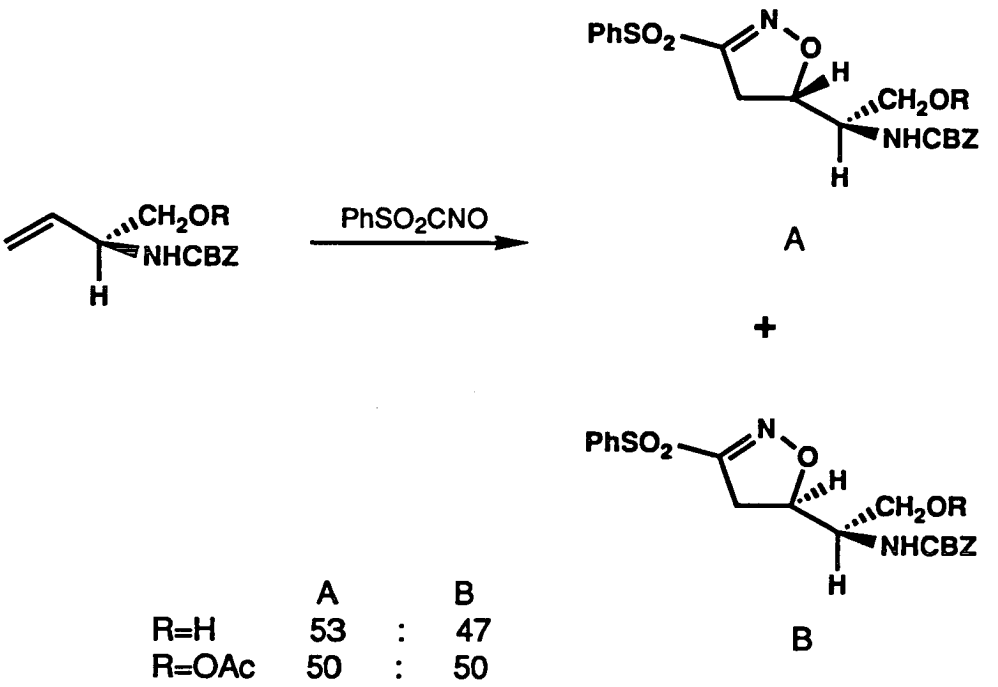


Fig 23

A ratio of 53:47 was reported for this reaction (also determined by isolation). This is almost identical to the ratio observed in the present work for the cycloaddition reaction of olefin **(13)** with ethoxycarbonylformonitrile oxide, another electron deficient 1,3-dipole. These workers claim that there is no evidence for hydrogen bonding being involved, based on the small difference in selectivity on changing from the exposed hydroxyl function to the acetate derivative (*ca.* 5%) (scheme 34). However, in the present work changing from the five membered oxazolidine ring, in which the alcohol moiety is masked, to the

N-protected amino-alcohol results in a greater change in π-facial selectivity (68:32 to 46:54). It is tentatively suggested that this could be the result of a hydrogen bonding interaction in the transition state involving the acyclic alkene **(13)**.



	A		B
R=H	53	:	47
R=OAc	50	:	50

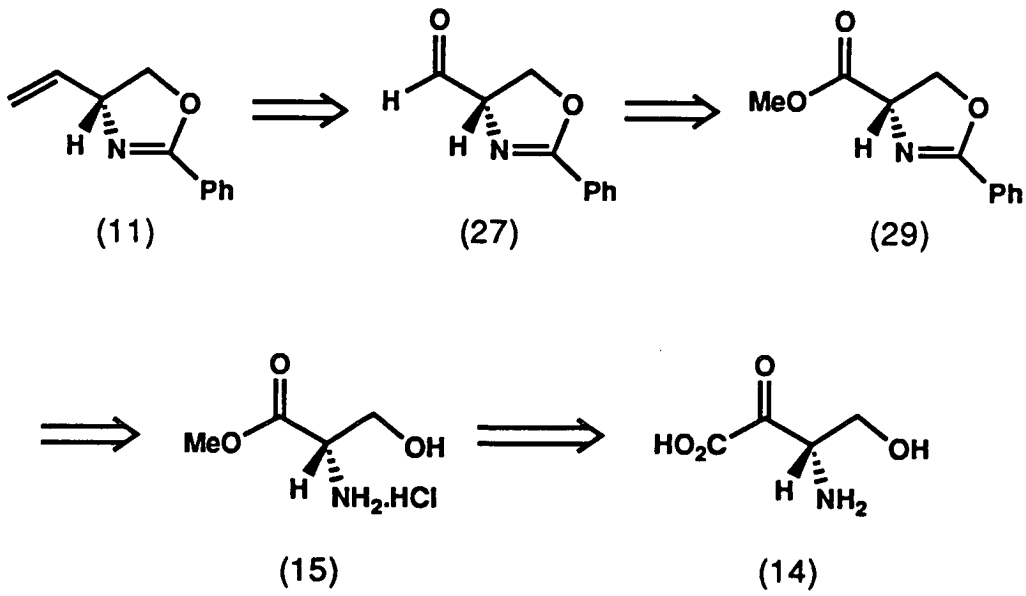
scheme 34

2.1.6. Synthesis of 2-phenyl-4-vinyl-4,5-dihydro-oxazole (11).

The synthetic route to the title alkene was envisaged to proceed *via* the 4-formyloxazoline (dihydro-oxazole) **(27)** which has been used previously as a protected β-amino-alcohol in the synthesis of some cerebrosides (glycosphingolipids)[107 108]. This compound was especially attractive, since it provided not only a route to the chiral olefin **(11)**, but also to the asymmetric oxime **(28)**, which would in turn be a source of the nitrile oxide. The proposed strategy is outlined in scheme 35.

Treatment of benzonitrile in ether/ethanol with HCl gas afforded ethyl benzimidate hydrochloride in 91% yield. Reaction of the imino ether with (*S*)-serine methyl ester hydrochloride **(15)**, according to the procedure described by Thornton,[107] furnished oxazoline **(29)** in 72% yield after chromatography. Attempts to reduce the oxazoline ester to the corresponding aldehyde by the procedure reported in the literature[107 109] were only partly successful. ^{1}H-NMR analysis of the crude reaction mixture indicated only a 20% conversion to the aldehyde (δH: C*H*O, 9.8ppm, *Me*O_2C, 3.4ppm). No attempt was made to isolate the aldehyde by chromatography as it has been reported to be very unstable at room temperature.[107-109] Attempts to improve the yield by modifying the reaction conditions (temperature, solvent, quantity of DIBAL) proved unsuccessful. Instead, the ester was reacted with lithium aluminium hydride (LAH) in ether providing the oxazoline-4-methylalcohol **(30)**. The literature procedure for this conversion[110] emphasises the importance of using half an equivalent of the reducing agent to avoid reduction of the oxazoline ring. When these conditions were employed yields were low and incomplete consumption of the ester was observed by tlc. This suggests that reduction of the heterocyclic ring was competing with reaction at the ester moiety. Enhanced yields (71% after recrystallisation)

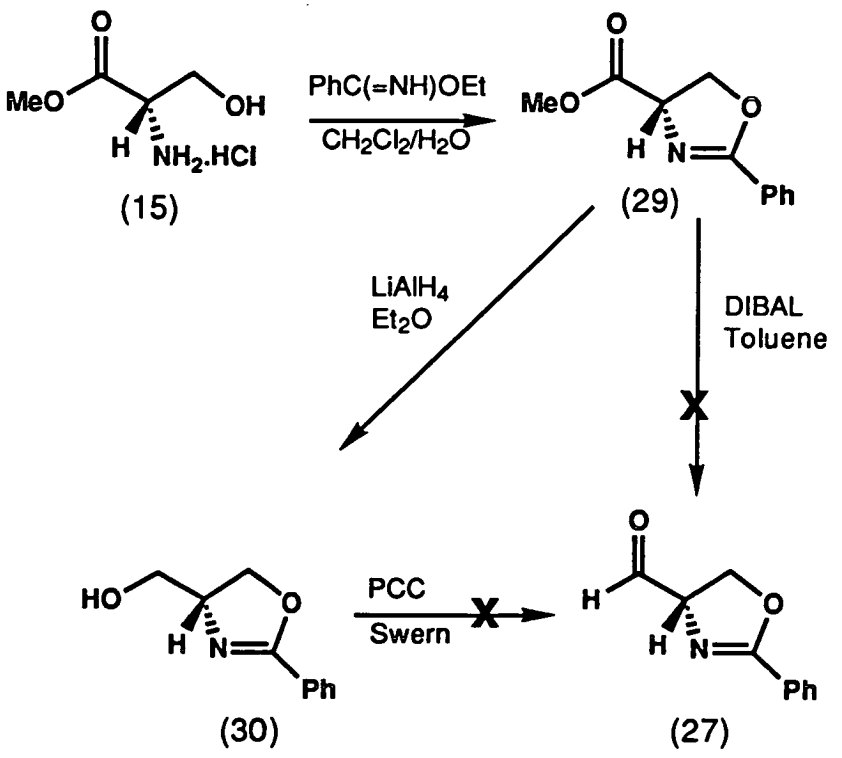
were obtained after modification of the literature procedure. An excess of LAH (2 equivs.) was suspended/dissolved in ether under an argon atmosphere and the oxazoline ester (**29**) added rapidly. After stirring for no more than 5 minutes the reaction was quenched and worked up.



scheme 35

Attempted oxidation of the alcohol (**30**) with pyridinium chlorochromate (PCC)[111] failed to produce any aldehyde (^{1}H-NMR); this may have been due to the extended reaction time required for complete consumption of the starting material (5 hours), given that the formyl-oxazoline is unstable at room temperature. In the light of this result it was reasoned that low temperature oxidation of the alcohol might prove more fruitful and a Swern oxidation[112] (DMSO,Et_3N, oxalyl chloride, -60°C) was attempted. Again ^{1}H-NMR analysis of the crude reaction product showed only a very small amount of aldehyde to be present. It is worth noting that as the reaction mixture warmed to room temperature it changed from a clear to a yellow solution, possibly due to decomposition of the aldehyde. This work

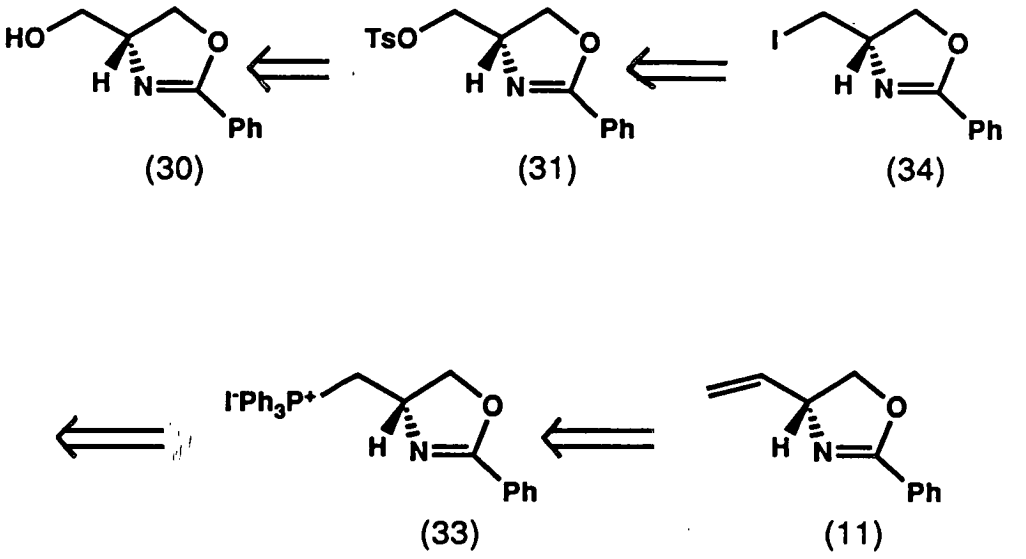
is summarised in scheme 36.



scheme 36

At this point the strategy was reversed; instead of using the oxazoline as the aldehyde partner in the Wittig reaction, it was used to provide the phosphonium moiety (scheme 37). Treatment of the hydroxymethyl oxazoline **(30)** with *p*-toluenesulphonyl chloride in pyridine on a small scale (*ca.* 100mg) afforded the tosylate **(31)** in 63% yield after chromatography. However, attempts to repeat the reaction on a larger scale (*ca.* 3g) furnished only 3% of the required tosylate, along with an unidentified major product.

The low yield of the tosylated alcohol necessitated the development of an alternative approach to provide a leaving group which would facilitate elaboration of the exocyclic methylene. To this end the hydroxymethyl



(30) (31) (34)

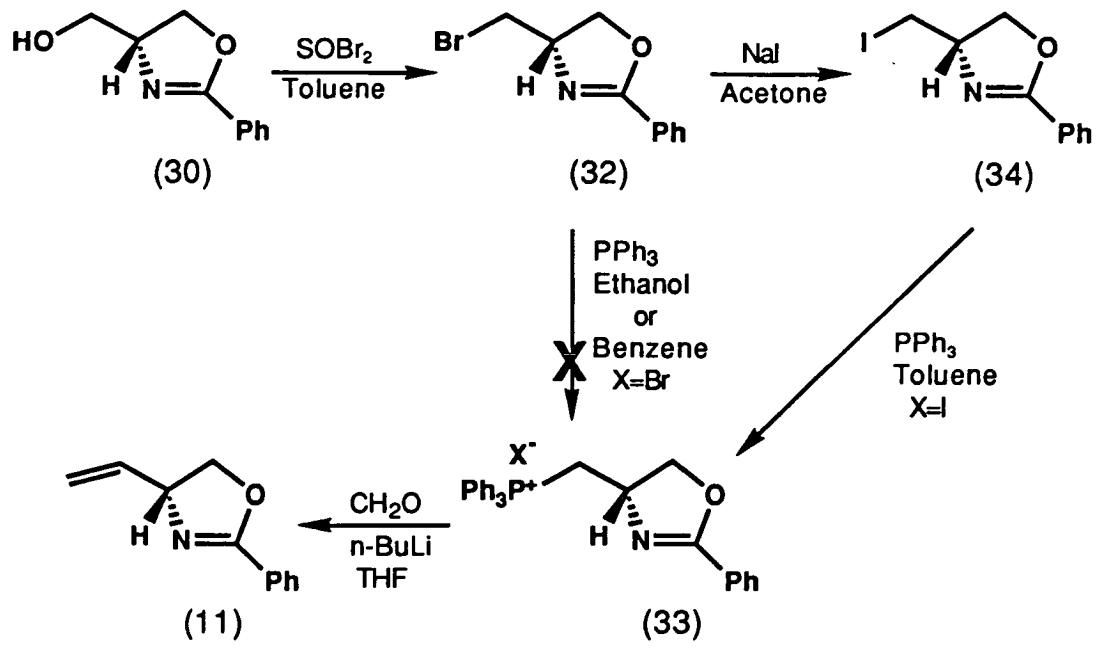
(33) (11)

scheme 37

oxazoline **(30)** was converted to the 4-bromomethyl analogue **(32)** in 70% yield using thionyl bromide in toluene. Conversion of **(32)** to the phosphonium salt **(33)** (X=Br) by reaction with triphenylphosphine, failed in both polar (ethanol), and non-polar (benzene) solvents. The bromomethyl oxazoline **(32)** was therefore converted to the iodo analogue **(34)** (83% after purification) by treatment with sodium iodide in refluxing acetone. The iodomethyl heterocycle was reacted with triphenylphosphine in refluxing toluene, furnishing the phosphonium salt **(33)** (X=I) in quantitative yield as an off white powder. Reaction of **(33)** with butyllithium in THF followed by quenching of the ylide with formaldehyde provided the required 4-vinyloxazoline **(11)** in 50% yield after chromatography. The synthesis of **(11)** is summarised in scheme 38.

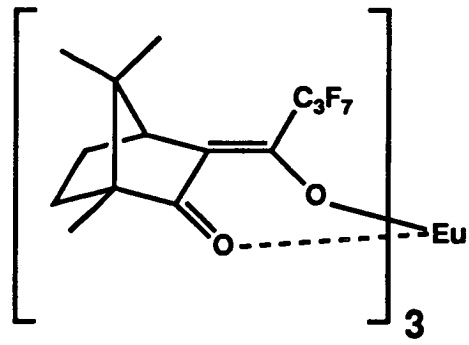
2.1.7. Racemisation of Oxazoline Alkene (11).

To check the chiral integrity of the vinyl oxazoline **(11)** a ^{1}H-NMR chiral shift experiment was carried out. The chiral shift reagent chosen was



scheme 38

tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato],europium (III) (**35**), which was added in portions of 3 mol% at a time. The ^{1}H-NMR spectrum was recorded after each addition. Figure 24 shows clearly, not only the change in chemical shift of the peaks due to the shift reagent, but also the gradual separation of some of the signals. This established that the vinyl oxazoline (**11**) had undergone racemisation of its chiral centre and the integration (Fig. 25) indicated that (**11**) was a *ca.* 1:1 mixture of enantiomers.



(35)

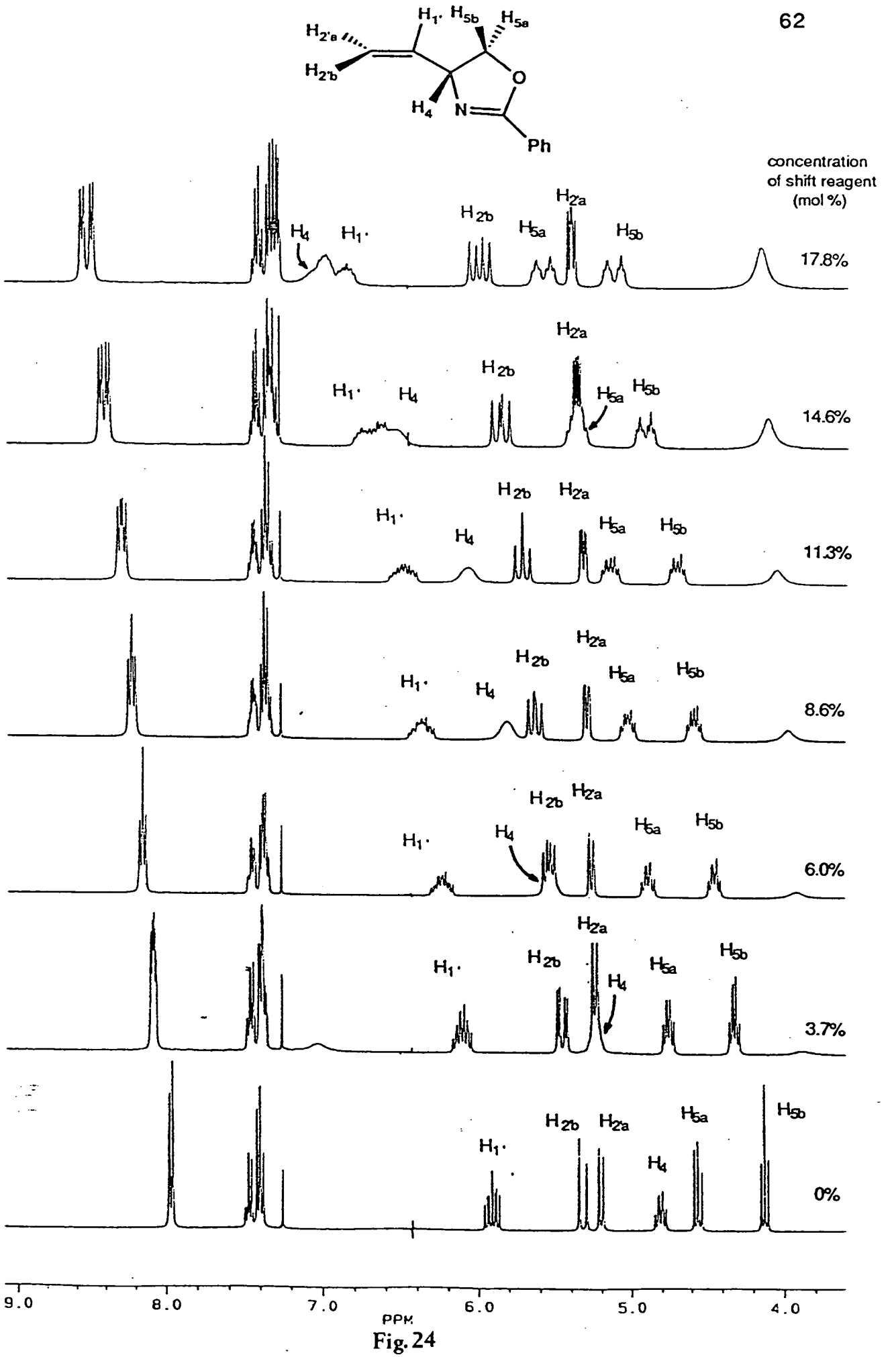

H1· H5b H5a
H2'a
H2'b
O
H4
N
Ph
concentration of shift reagent (mol %)
17.8%
14.6%
11.3%
8.6%
6.0%
3.7%
0%
9.0
8.0
7.0
6.0
5.0
4.0
PPM

Fig. 24

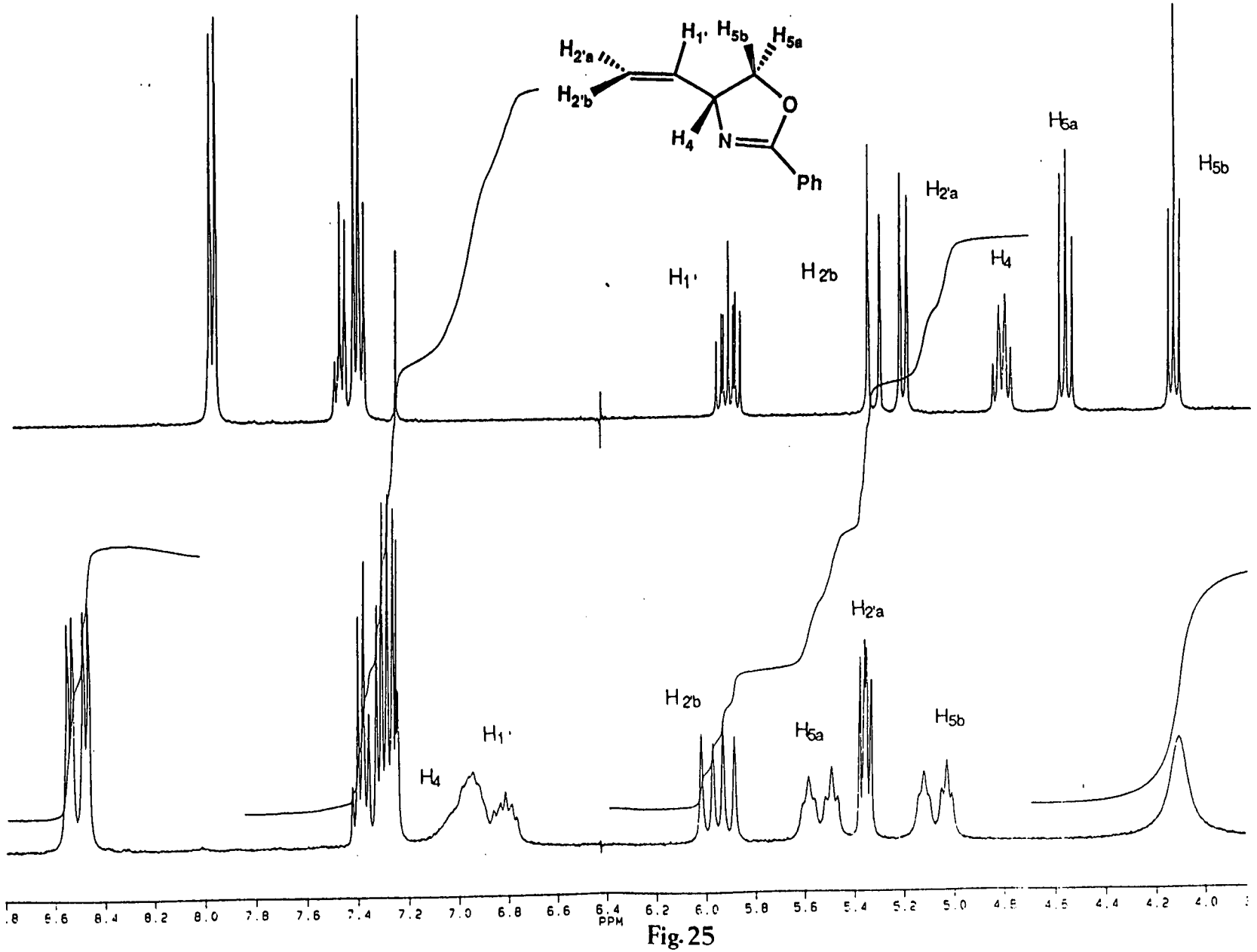
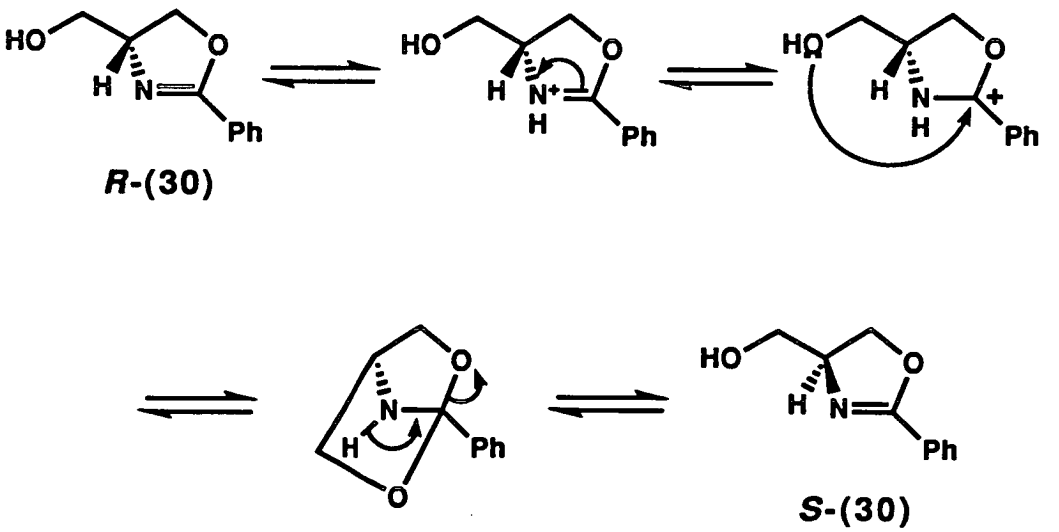

concentration of shift reagent (mol %)
0%
17.8%
H1'
H2'a
H2'b
H4
H5a
H5b
Ph
O
N
PPM

Fig. 25

The initial hypothesis was that the racemisation was occuring under the strongly basic conditions of the Wittig reaction (BuLi). Repeating the olefination using both potassium-*t*-butoxide and potassium carbonate/18-crown-6, as replacements for the butyllithium, also gave 1:1 enantiomeric mixtures in both cases. While the basic conditions of the Wittig reaction seemed the most likely cause of racemisation, the low optical rotation observed for 4-bromomethyl-2-phenyl-4,5-dihydro-oxazole **(32)** ($[\alpha]_D$ (20°C) +3.4° (c 1.0 in $CHCl_3$) meant that an alternative measure of its chiral integrity had to be obtained. A similar ^{1}H-NMR experiment with the same shift reagent was carried out (Fig. 26), which clearly showed that the bromomethyl oxazoline **(32)** had undergone complete racemisation under the conditions employed for its formation ($SOBr_2$, toluene).



***R*-(30)** ⇌ ⇌ ***S*-(30)**

scheme 39

The explanation may lie in the acidic and anhydrous nature of the reaction. Protonation of the ring nitrogen may render C_2 vulnerable to attack by the hydroxyl function (scheme 39). This hypothesis suggests that hydroxymethyloxazoline **(30)** undergoes racemisation before

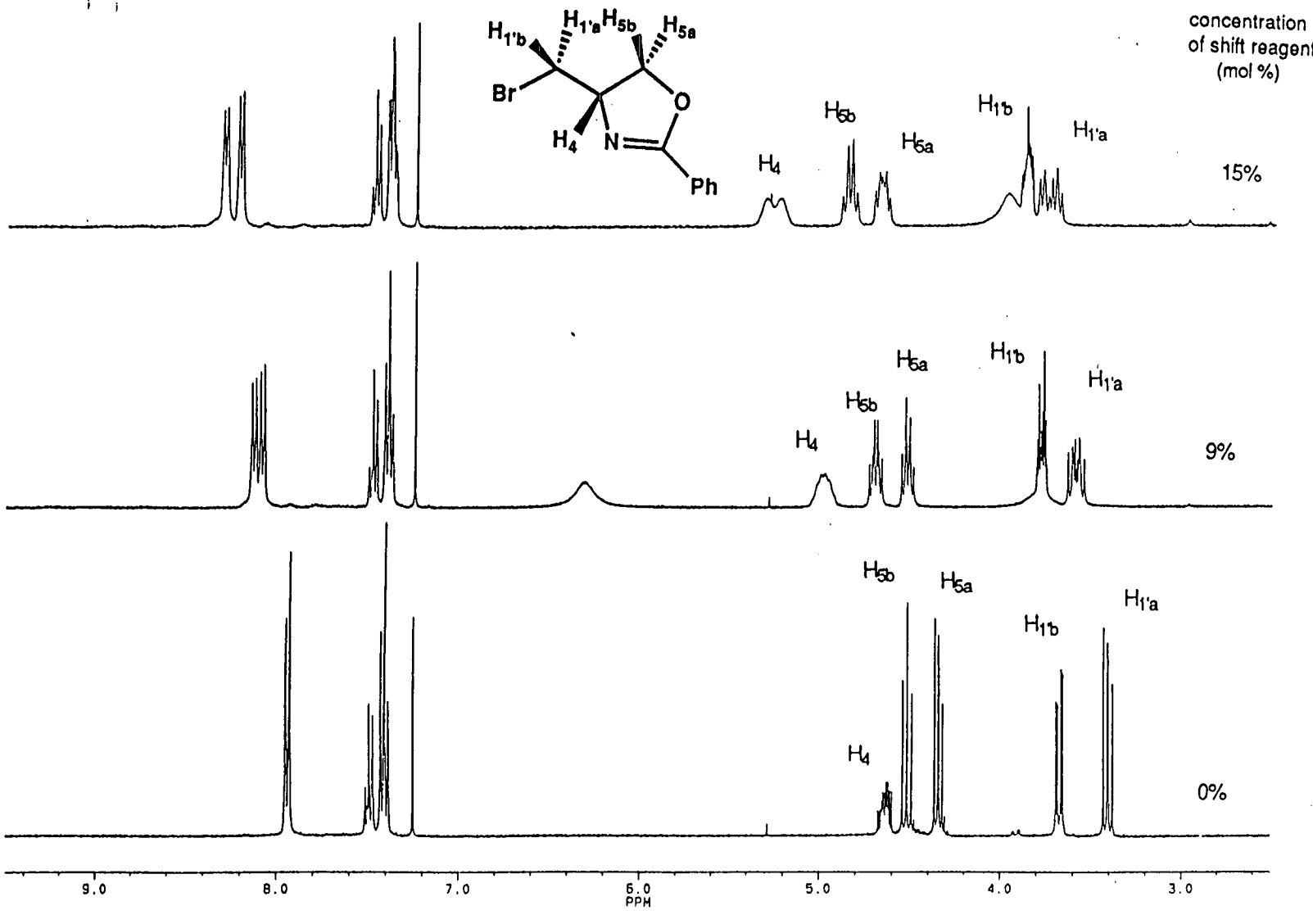

concentration
of shift reagent
(mol %)
15%
9%
0%
Br
O
N
Ph
H4
H1'b
H1'a
H5b
H5a
9.0
8.0
7.0
6.0
5.0
4.0
3.0
PPM

Fig. 26

conversion to the bromomethyl heterocycle **(32)**.

This process would explain the racemisation of the oxazoline under acidic conditions. Both enantiomers can then undergo reaction with the thionyl bromide to give the racemic bromomethyloxazoline **(32)**.

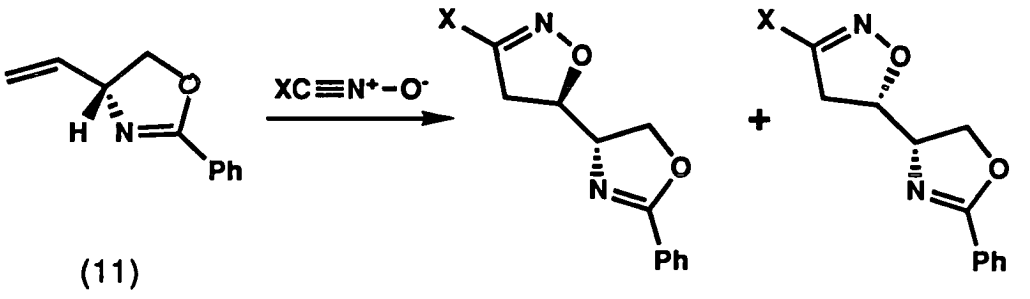
2.1.8. Cycloaddition Reactions of Nitrile Oxides with (*R/S*) 2-phenyl-4-vinyl-4,5-dihydro-oxazole (11).

Despite the racemic nature of the dipolarophile, cycloaddition reactions were carried out to determine the levels of π-facial selectivity which could be achieved for such a heterocyclic system, in which the allylic nitrogen is sp^2 hybridised. The nitrile oxides studied (PhCNO, EtO_2CCNO, BrCNO) were those previously used to investigate the corresponding reaction with vinyl-oxazolidine **(12)**. All of the cycloaddition reactions were performed at room temperature in the same manner as previously described, the triethylamine being added over 15-21 hours by means of a motorised syringe pump. The diastereomeric products were purified and separated by flash column chromatography or preparative thin layer chromatography. The results of these reactions are summarised in scheme 40 (only one enantiomer of each compound is shown).

The yields of cycloadducts varied from 88% for benzonitrile oxide to 65% for ethoxycarbonyformonitrile oxide. The lower yield in the latter reaction probably reflects the greater propensity of EtO_2CCNO, an electron deficient nitrile oxide, to undergo dimerisation as a side reaction.[113 114] The yield of adduct isolated from the cycloaddition of bromonitrile oxide with **(11)** was poor (29%), due, in part at least, to problems encountered in the work up.

The *erythro/threo* ratios presented in scheme 31 were obtained by isolation of the adducts by chromatography and by HPLC analysis of

portions of the crude reaction mixture. The identity of the peaks in the HPLC analysis was confirmed by peak enhancement using the isolated and characterised products. The HPLC results are in reasonable agreement with the isolated ratios.



(11)

(a) *Erythro*

(b) *Threo*

Compound	X	Yield	RATIO HPLC (isolated)		HPLC (isolated)	
(26)	Ph	88%	76	(69)	24	(31)
(36)	EtO_2C	65%	82	(80)	18	(20)
(37)	Br	29%	69	(69)	31	(31)

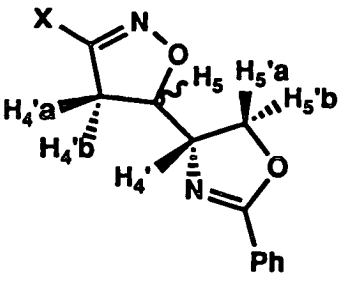
scheme 40

2.1.9. Some Observed Trends in the Characteristics of the Cycloadducts.

In tlc analysis and chromatographic separations of the diastereomer mixtures (SiO_2, EtOAc/hexane eluents) the minor *threo* isomer was always the more polar of the two.

In the ^{1}H-NMR spectra of the adducts the isoxazoline H_5 signals of the *threo* products occur at higher frequencies than the corresponding protons of the *erythro* adducts (table 3).

Table 3. ^{1}H-NMR Chemical shifts (ppm) of selected hydrogens from the cycloadducts of 2-phenyl-4-vinyl-4,5-dihydro-oxazole **(11)** (C_6D_6).



	H_{4a}[1]		H_{4b}[1]	
X	*Erythro*	*Threo*	*Erythro*	*Threo*
Ph	3.23 (3.30)[2]	3.05 (3.39)[2]	2.89 (3.13)	2.69 (3.30)
EtO_2C	3.16	3.22	2.85	2.70
Br	2.89	2.88[5]	2.57	2.49[5]

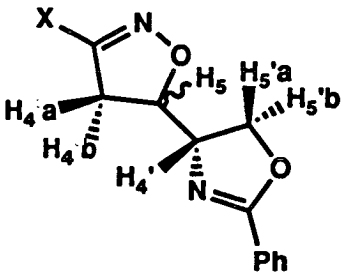
	H_5		$H_{4'}$	
X	*Erythro*	*Threo*	*Erythro*	*Threo*
Ph	4.27 (4.37)	4.59 (5.07)	-----[3] (4.2)[4]	4.2[4] (4.71)
EtO_2C	4.17	4.25	3.8[4]	3.85
Br	-----[3]	4.21[5]	3.9[4]	3.90[5]

	$H_{5'a}$[1]		$H_{5'b}$[1]	
X	*Erythro*	*Threo*	*Erythro*	*Threo*
Ph	-----[3] (4.24)	-----[3] (4.48)	4.15 (4.13)	3.88 (4.41)
EtO_2C	-----[3]	4.0[4]	-----[3]	3.73
Br	-----[3]	-----[3]	3.99[5]	3.80[5]

1. Arbitarily assigned.
2. Figures in brackets are for samples run in $CDCl_3$.
3. Not determined.
4. Approximate values, peaks not fully resolved.
5. $CDCl_3/C_6D_6$.

The coupling constants between the two ring methines (H_5 and $H_{4'}$) (table 4) appear to be larger in the *erythro* compounds (8Hz) than the corresponding values for the *threo* adducts (*ca.* 3Hz), although this could not be unequivocally confirmed as the H_5 signals for **(36a)** and **(37a)** were not sufficiently well resolved to permit detailed analysis.

Table 4. Selected coupling constants for the cycloadducts of 2-phenyl-4-vinyl-4,5-dihydro-oxazole **(11)**.



	$J_{H4a\ H4b}$ (Hz)		$J_{H4a\ H5}$ (Hz)	
X	*Erythro*	*Threo*	*Erythro*	*Threo*
Ph[1]	17.0	16.9	6.4	10.9
Ph[2]	17.0	16.7	6.3	7.9
EtO_2C[2]	17.9	17.4	7.9	7.9
Br[2]	17.4	17.1	6.3	7.5

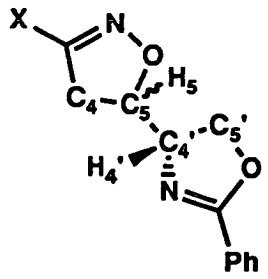
	$J_{H4b\ H5}$ (Hz)		$J_{H5\ H4'}$ (Hz)	
X	*Erythro*	*Threo*	*Erythro*	*Threo*
Ph[1]	10.3	8.2	8.4	3.8
Ph[2]	10.3	11.2	----[3]	3.3
EtO_2C[2]	10.9	11.6	----[3]	2.9
Br[2]	9.9	11.0	----[3]	2.4

1. $CDCl_3$
2. C_6D_6
3. Not determined.

The ^{13}C-NMR spectra of these compounds show that the chemical shift values of the isoxazoline C_4 and C_5 and the oxazoline $C_{4'}$ and $C_{5'}$ occur at lower frequency for the threo isomers (table 5).

These trends should allow the structures of future examples to be assigned with confidence.

Table 5. Selected ^{13}C-NMR chemical shift values for the cycloadducts of 2-phenyl-4-vinyl-4,5-dihydro-oxazole **(11)**

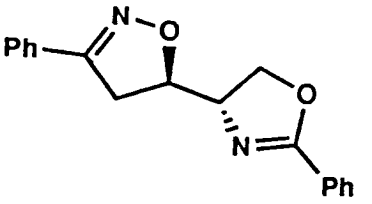


	Erythro				*Threo*			
X	C_4	C_5	$C_{4'}$	$C_{5'}$	C_4	C_5	$C_{4'}$	$C_{5'}$
Ph	38.8	82.9	69.6	70.7[1]	36.2	81.2	68.5	68.7[1]
EtO_2C	37.6	85.2	69.9	70.3[2]	-----	-----	-----	-----[3]
Br	45.2	83.3	69.2	70.4[1]	43.1	81.7	68.3	68.6[4]

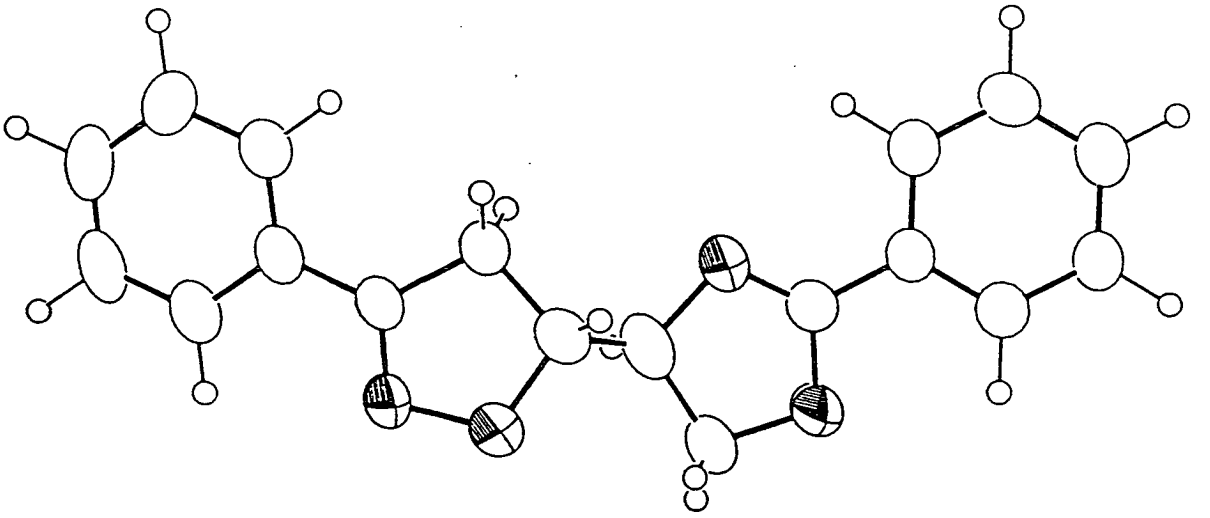
1. $CDCl_3$. 2. C_6D_6. 3. Not determined. 4. $CDCl_3/C_6D_6$

2.1.10. Assignment of Stereochemistry.

The stereochemistry of the adducts formed in the cycloaddition of the three nitrile oxides with (*R/S*)-2-phenyl-4-vinyl-4,5-dihydro-oxazole **(11)** was made on the basis of an *X*-ray crystal structure (Fig 27) obtained on the major isomer formed in the reaction with benzonitrile oxide. This proved to be the *erythro* (*RS/SR*) product. The stereochemistry of the adducts of ethoxycarbonylformonitrile oxide and bromonitrile oxide were assigned by analogy with this observation. The crystal structure shows



26a



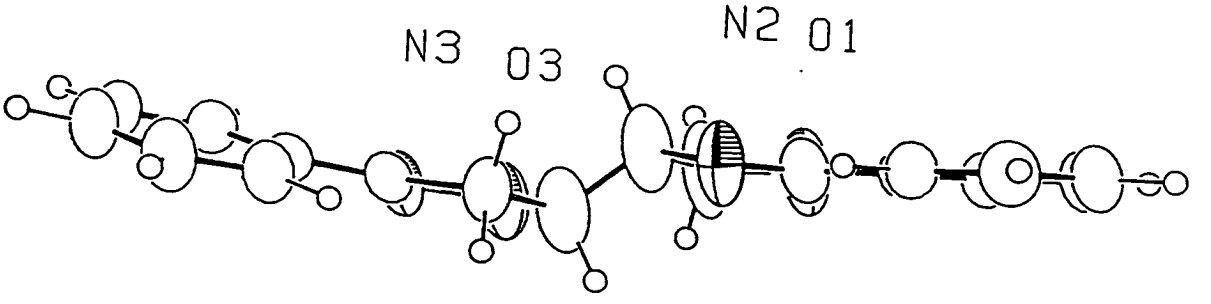


Fig. 27

that the heterocyclic rings are nearly planar, and that there is a step between the two heterocyclic ring methines.

2.1.11. Explanation for the Observed Stereoselectivities.

By analogy with the work of Houk and co-workers[71] on the energies of the six possible staggered transition states for the cycloaddition reactions of nitrile oxides with 3-methoxy-1-butene, six equivalent transition states can be drawn for the reaction of (*R/S*)-2-phenyl-4-vinyl-4,5-dihydro-oxazole (**11**) with the same 1,3-dipoles (Fig 28).

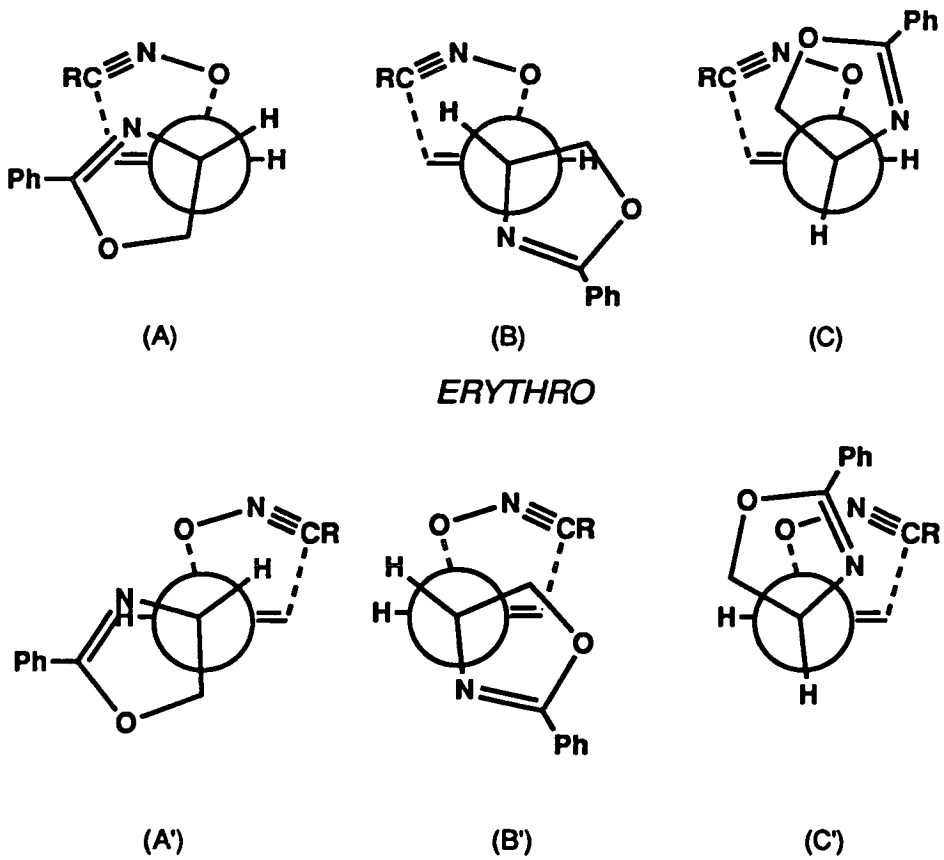


Fig 28

Using 3-methoxy-1-butene as a model Houk has predicted that the highest energy, and therefore least favourable, transition state which gives rise to the *erythro* product is the one which positions hydrogen *anti* to the forming C-O σ-bond and the alkoxy in the "outside" position (Fig 29A). The highest energy transition state on the pathway to the *threo* adduct is thought to be the one which locates the alkoxy function *anti* to the forming C-O σ-bond, thus destabilising the electron deficient transition state by electron withdrawal *via* the COσ* orbital; the hydrogen takes up the "outside" position (Fig 29B).

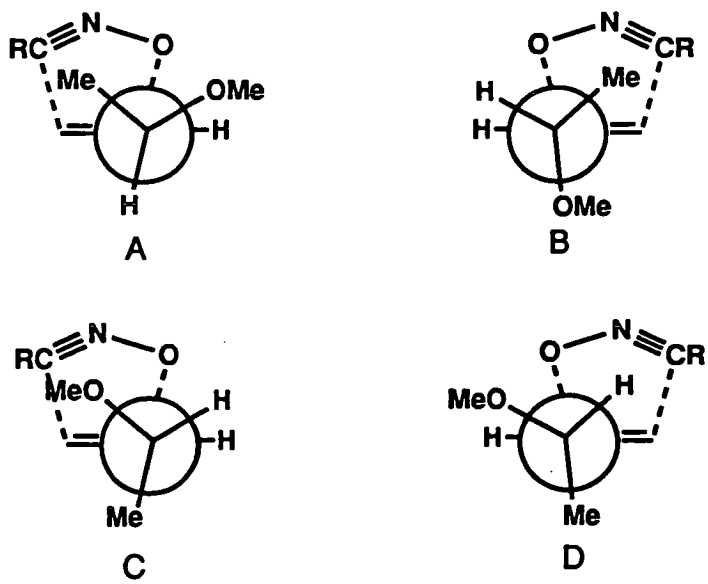


Fig. 29

The most important transition state which leads to the *erythro* product is calculated to be the one in which the alkoxy substituent occupies the "inside" position (Fig 29C), while the second most important is that in which the alkoxy is in the "outside" position (Fig 29D); this affords the *threo* adduct.

Curran[106] has reported the results of cycloadditions of nitrile oxides with

chiral (α-oxyallyl)-silanes. He rationalises the outcome of these reactions on a purely steric basis for which he uses the Houk steric model.[72] In this work the transition states which places the hydrogen *anti* with respect to the forming C-O bond, i.e. in the position favoured by the largest group, are considered unimportant.

The cycloaddition reactions of nitrile oxides with 2-phenyl-4-vinyl-4,5-dihydro-oxazole (**11**) are believed to be the first examples of nitrile oxide cycloadditions involving a chiral alkene which possesses an allylic sp^2 hybridised nitrogen. The observed stereoselectivities will be considered first on a purely steric basis and the significance of a stereoelectronic contribution will then be evaluated.

In a steric model for the cycloaddition reaction of nitrile oxides with olefin (**11**) the two transition states which place hydrogen *anti* with respect to the forming C-O bond[106] (**C** and **C'**) (Fig. 28) are ignored as this position is likely to be occupied by the largest group.

Of the two transition states (**A** and **B**) which give rise to the major *erythro* adduct, **A** appears to be the most favourable; the larger $-CH_2O-$ group is in the *anti* alignment and the smallest group, hydrogen, is in the more sterically demanding "outside" position. The alternative transition state on route to the *erythro* product (**B**) is a less likely option as the largest group $-CH_2O-$ is positioned in the most sterically demanding "outside" alignment.

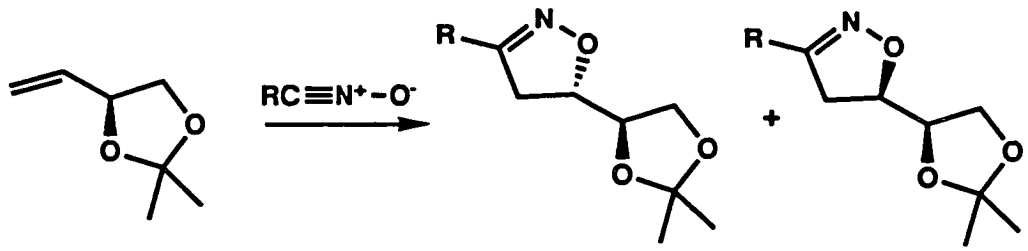
Considering now the two transition states which could give rise to the *threo* products (**A'** and **B'**): **B'** is considered to be the least favourable as it places the largest group in the "inside" position with the nitrogen *anti* to the forming C-O bond. **A'**, which locates the $-CH_2O-$ *anti*, with the nitrogen "outside" and the hydrogen "inside" is predicted to be the most favourable of the two on steric grounds. Thus the *erythro* product is predicted to arise

from transition state **A**, whereas the *threo* adduct is thought to form *via* transition state **A'**, which only involves a reversal of the "inside" and "outside" groups. However, the relatively small difference in size between the nitrogen and the -CH_2O- group means that a contribution from **B'** when considering a purely steric transition state model cannot be ruled out. These predictions are in line with those made by other workers in the field.[72 106]

The involvement of a stereoelectronic effect, similar to that advocated for allylic alkoxy substituents,[71] exerted by the allylic sp^2 hybridised nitrogen is now considered. In the absence of any theoretical calculations on this system the conclusions are based on comparisons of the face selectivities observed in nitrile oxide cycloadditions to vinyl-oxazoline (**11**) and similar reactions which are reported to derive their diastereoselectivities from the operation of the "inside alkoxy effect".

For example, the cycloaddition of benzonitrile oxide with (+)-(*S*)-isopropylidene-3-butene-1,2-diol has been reported[71 73] to occur in high yield with a π-facial selectivity ratio of 85:15 in favour of the *erythro* product. The corresponding reaction of ethoxycarbonylformonitrile oxide with the same olefin is also diastereoselective (80:20) (scheme 41). In the present work, the cycloaddition reactions of the same nitrile oxides with 4-vinyl-oxazoline (**11**) yielded diastereomeric products in the ratios of 82:18 (R=CO_2Et) (**36a** & **36b**) and 76:24 (R=Ph) (**26a** & **26b**), while the ratio for bromonitrile oxide with (**11**) was 69:31. The diastereofacial selectivities of the reactions of the vinyl-oxazoline (**11**) are thus of the same order as those observed in a system where the stereoelectronic effect is considered to be operating. It is therefore concluded that the sp^2 nitrogen avoids the *anti* position for similar reasons to an allylic alkoxy function, namely to minimise electron withdrawal from the electron

deficient transition state *via* a CNσ* interaction with the π-system.



	Erythro	*Threo*
R=Ph	85	15
$R=CO_2Et$	80	20

scheme 41

This observation is in accord with the hypothesis based solely on steric arguments, namely, that the important transition states involved in the formation of the *erythro* and *threo* products are **A** and **A'** respectively (Fig. 28). The cycloaddition of (**11**) with bromonitrile oxide (69:31) is as good as the best selectivity reported for a nitrile oxide cycloaddition to an olefin with a nitrogen substituent at an α-chiral centre (70:30).[96-100] The ratios observed with benzonitrile oxide and ethoxycarbonylnitrile oxide are the highest which have been reported for this class of dipolarophile (PhCNO, 76:24; EtO_2CCNO, 82:18). The spread of π-facial selectivity results observed in this series of reactions is not inconsistent with previous reports.[71 73]

2.1.12. Conclusion.

2.1.12.1. Summary of Results.

The 4-vinyl-oxazolidine (**12**) was prepared by the literature procedure, with some modifications, from (*S*)-serine, and was used in cycloaddition

reactions with three nitrile oxides. Yields of cycloadducts were very good, however, π-facial selectivity was only moderate (*ca.* 66:34), the *erythro* (5*R*,4'*S*) products were favoured. The observed π-facial induction is approaching the best which have been reported for olefins with an α-chiral centre bearing an allylic nitrogen substituent.[96-100] The isoxazoline adducts were separated after deacetonisation.

The stereochemical bias was explained on the basis of a steric transition state model.

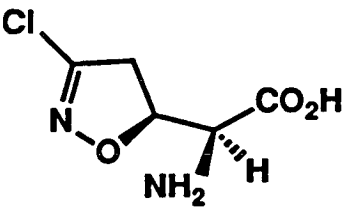
The 4-vinyl-oxazoline **(11)** was prepared in racemic form after an unexpected racemisation during its synthesis. Nitrile oxide cycloaddition reactions furnished the bis-heterocyclic products in poor to good yield; π-facial selectivities varied from (69 : 31, BrCNO) to (82:18, EtO_2CCNO) (by HPLC analysis of the reaction mixture). The isomer ratios for the reaction with benzonitrile oxide and ethoxycarbonylformonitrile oxide are the best which have been achieved for a chiral olefin with an allylic nitrogen substituent. The stereoinduction was accounted for by both steric and stereoelectronic factors.

The acyclic alkene **(13)** gave low π-facial selectivities; the major isomer had the (5*S*,4'*S*) configuration. The reversal of π-facial induction was explained on the basis of a more favourable hydrogen bonding interaction, between the free hydroxyl function and the nitrile oxide oxygen, in the transition state which leads to the (5*S*,4'*S*) product.

2.1.12.2. Future Work.

The cycloadducts of the heterocyclic olefin **(12)** provide a potentially useful intermediate for the synthesis of the antimetabolite antitumor antibiotic acivicin **(38)** which possess the (5*S*,α*S*) configuration. Acivicin

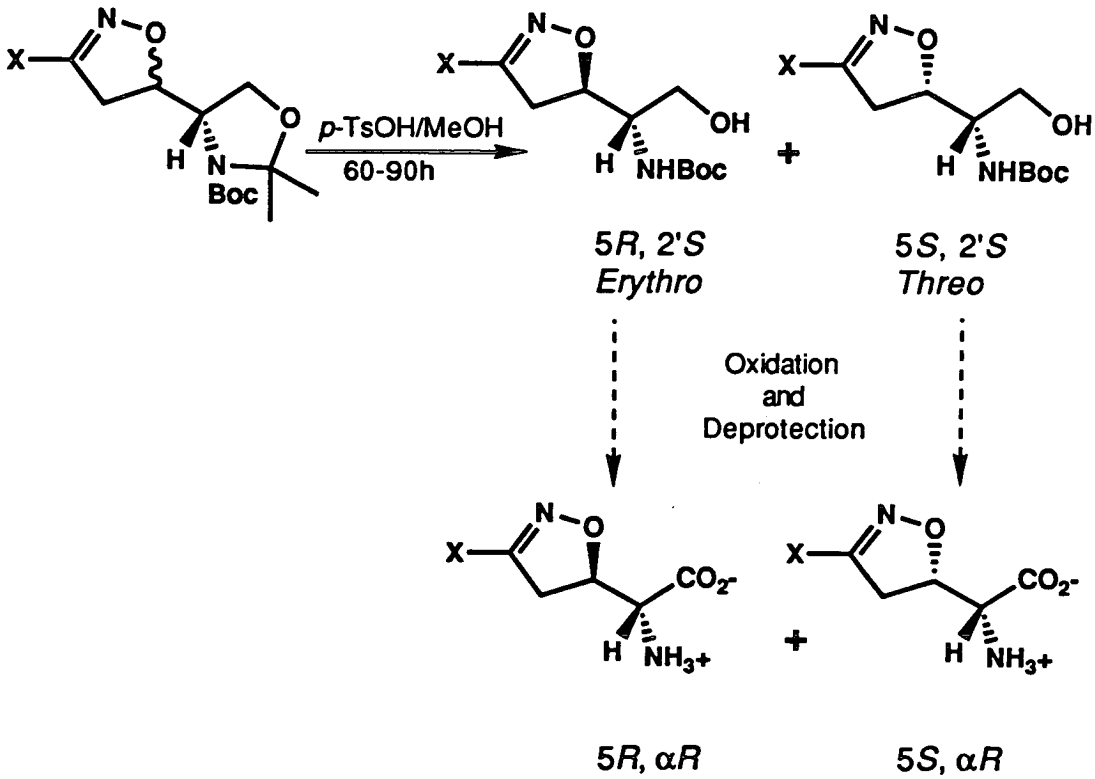
was first isolated from *Streptomyces sviceus* in 1973,[115] and has now entered phase two clinical trials for synergistic combination chemotherapy. Several syntheses of acivicin have been reported.[96-99,116-121] The most concise approach to this densely functionalised amino acid involves the cycloaddition reaction of chloronitrile oxide with vinyl glycine, however Baldwin and co-workers[117] failed to achieve this coupling. Wade *et al*[97] did manage to bring about the cycloaddition of the same nitrile oxide with *N*-phthalylvinylglycine by generating the 1,3-dipole from phosgeneoxime on treatment with an excess of silver nitrate. The main disadvantage of all the reported nitrile oxide cycloaddition approaches to acivicin[96-99] is that the major isomer possesses the wrong configuration.



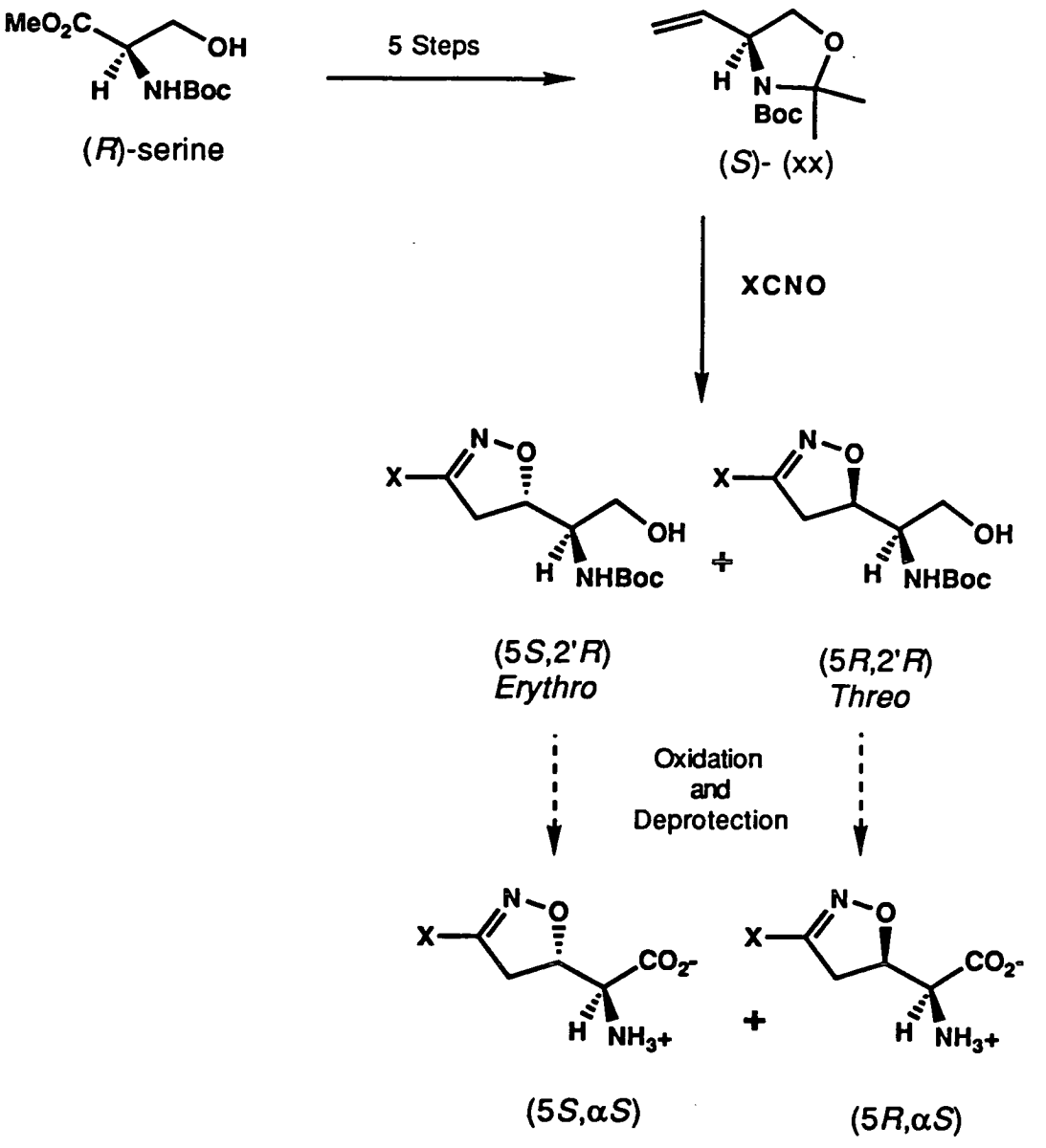
(38)

In the present work the partially deprotected aminoalcohols **(22)**, **(23)** and **(24)** only require oxidation and deprotection (scheme 42) to furnish isomers of acivicin and other 3-substituted analogues.

In order to arive at the correct, (5*S*,α*S*) configuration, the (5*S*,4'*R*) cycloadduct would be required, this is available from the (4*S*)-vinyl-oxazolidine which can be prepared from (*R*)-serine. This approach, if successful, would be the first nitrile oxide cycloaddition approach to acivicin, and its analogues, which yields the major adduct with the correct configuration. The proposed approach is outlined in scheme 43.


X
N
O
H
N
Boc
p-TsOH/MeOH
60-90h
OH
NHBoc
+
5R, 2'S
Erythro
5S, 2'S
Threo
Oxidation
and
Deprotection
CO2-
NH3+
5R, αR
5S, αR

scheme 42


MeO2C
OH
H
NHBoc
(R)-serine
5 Steps
O
H
N
Boc
(S)- (xx)
XCNO
X
N
O
OH
H
NHBoc
+
(5S,2'R)
Erythro
(5R,2'R)
Threo
Oxidation
and
Deprotection
CO2-
NH3+
(5S,αS)
(5R,αS)

scheme 43

2.2. Synthesis and Cycloaddition Reactions of Oxazoline- and Oxazolidine-4-carbonitrile Oxides.

2.2.1. Introduction

Two examples of heterocyclic nitrile oxides with asymmetric centres adjacent to the 1,3-dipolar moiety have been prepared. Both were derived from the readily available amino acid (*S*)-serine; the oxazolidine-4-carbonitrile oxide **(39)**, generated from the corresponding oxime **(40)** was enantiomerically pure. The oxazoline-4-carbonitrile oxide **(41)**, generated by the method of Mukaiyama[45] from the nitromethyl-heterocycle **(42)**, was racemic, due to an unexpected racemisation process during its synthesis (see sect. 2.1.7).

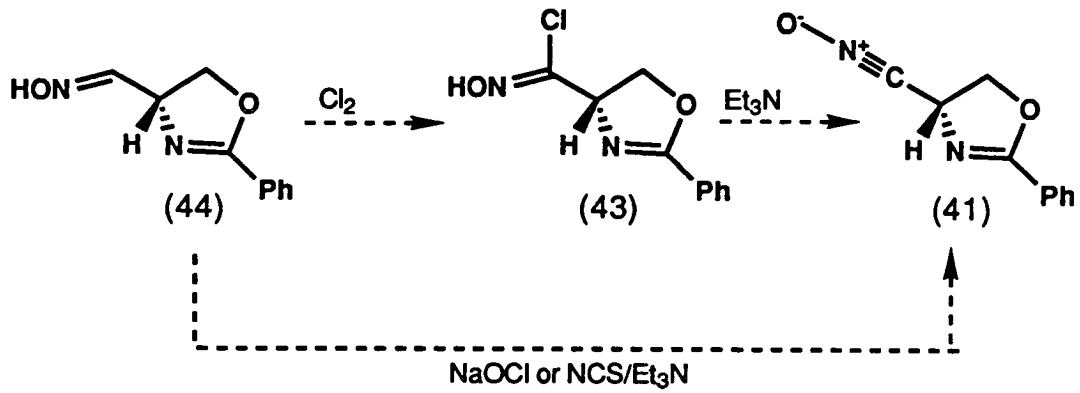
Both of the nitrile oxides represent chiral β-amino-alcohols, and as such provide a useful means of introducing that functionality into the 3-position of 2-isoxazolines, *via* 1,3-dipolar cycloaddition reactions. Exposure of the acyclic functionality masked by the 2-isoxazoline would facilitate the construction of densely functionalised hydrocarbon chains.

This work also allows a comparison to be made between the π-facial selectivities achieved for the heterocyclic olefins **(11)** and **(12)** and the corresponding nitrile oxides **(39)** and **(41)**.

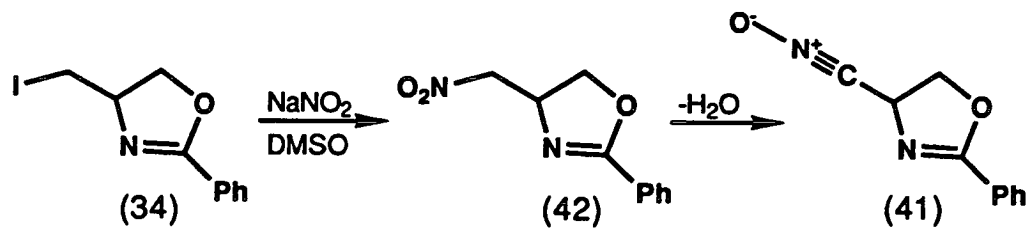
2.2.2. Synthesis of 4-nitromethyl-2-phenyl-4,5-dihydro-oxazole (42).

It was initially envisaged that the chiral nitrile oxide **(41)** would be generated from the hydroximoyl chloride **(43)** or by an *in situ* protocol directly from the oxime **(44)** (scheme 44). However, the aldehyde precursor proved difficult to prepare by the literature procedure[107] and an alternative approach had to be adopted. As nitromethyl compounds can be dehydrated to nitrile oxides by the procedure of Mukaiyama[45]

(scheme 45), (*R/S*)-4-iodomethyl-2-phenyl-4,5-dihydro-oxazole **(34)** , which had previously been used in the preparation of 4-vinyl-oxazoline **(11)**, was converted to the nitromethyl analogue **(42)** by treatment with sodium nitrite in DMSO (63%). As the iodomethyl heterocycle **(34)** is a racemic mixture the resulting nitrile oxide is also a mixture of isomers.



scheme 44

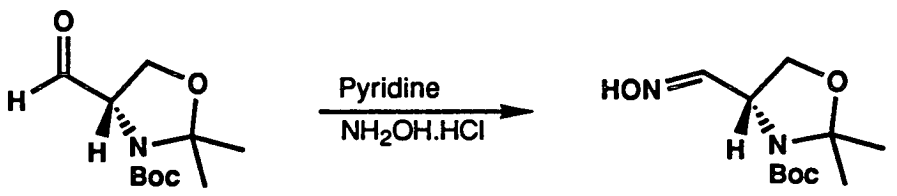


scheme 45

2.2.3. Preparation of (4*R*)-4-aldoximino-3-(*N*-*t*-butoxy-carbonyl)-2,2-dimethyloxazolidine (40).

The title oxime was prepared by treatment of the corresponding aldehyde **(18)** with hydroxylamine hydrochloride in pyridine in 40% yield after

chromatography. The low yield from this reaction was the result of using a fairly crude aldehyde preparation; this was because it was much easier to separate the oxime from the impurities present in the aldehyde than it was to purify the aldehyde (scheme 46).



(18) (40)

3:2 mixture of isomers

scheme 46

The ^{1}H-NMR spectrum of the purified oxime at room temperature (Fig.30A) ($CDCl_3$) shows most of the signals to be broad and poorly resolved, an effect attributed to a dynamic equilibrium between two conformations of the heterocyclic ring, similar to that observed for other compounds containing this type of ring system.[101 105] Warming the sample to 60°C (C_6D_6) brought about complete resolution of the spectrum (Fig. 30B). From this it is concluded that the oxime **(40)** exists as a mixture of *cis* and *trans* isomers in an approximate ratio of 2:3. The respective identities of the two isomers was not established, however, as this has no effect on the chlorination of the oxime which ultimately leads to one chloro-oxime isomer, the *Z*-form. This has been established for benzaldoxime, where chlorination of both the *E*- and *Z*-isomers gives rise to only the *Z*-hydroximoyl chloride.[122]

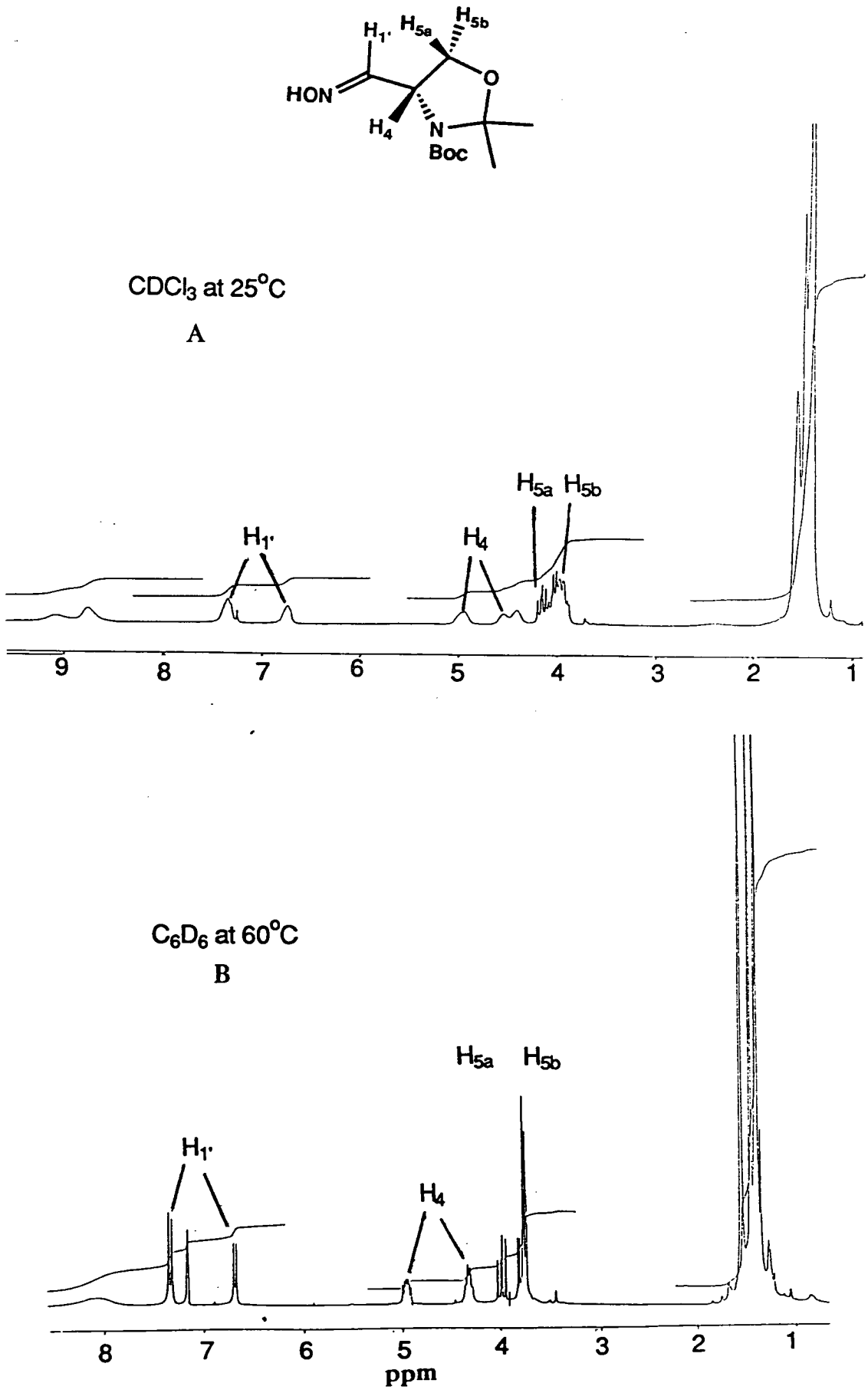
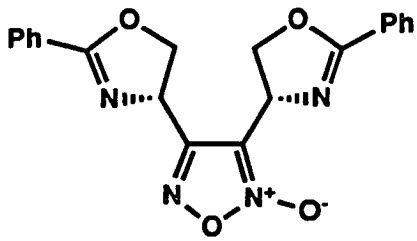

H1' H5a H5b
HON
O
H4
N
Boc
CDCl3 at 25°C
A
H5a H5b
H1'
H4
9 8 7 6 5 4 3 2 1
C6D6 at 60°C
B
H5a H5b
H1'
H4
8 7 6 5 4 3 2 1
ppm

Fig 30

2.2.4. Cycloaddition Reactions of (R/S)-2-phenyl-4,5-dihydro-oxazole-4-carbonitrile oxide (41).

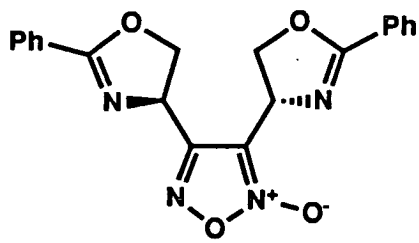
The title nitrile oxide **(41)** was generated from racemic 4-nitromethyl-2-phenyl-4,5-dihydro-oxazole **(42)** by the method of Mukaiyama.[45] When the cycloaddition was carried out with styrene as the dipolarophile, with all of the reagents being added at the beginning of the reaction (scheme 47, path A), the only isolable products were the two diastereomeric furoxans (furazan-N-oxides) **(45a)** and **(45b)**, which were recovered in a combined yield of 52% and readily separated by preparative tlc. The identity and stereochemistry of these compounds was confirmed by a single crystal *X*-ray structure of the slower eluting of the two isomers (Fig. 31). This showed it to be the *RR/SS* product **(45b)**; thus the faster eluting isomer is the *RS/SR* furoxan **(45a)**. While this reaction failed to produce any of the desired isoxazoline products due to the competing rapid dimerisation of the nitrile oxide, it did demonstrate that the 1,3-dipole was being generated under the reaction conditions. A modification of the procedure in which the nitromethyloxazoline **(42)** was added in a dropwise manner over four hours (scheme 47, path B) with the aid of a motorised syringe pump resulted in the formation of isoxazoline products along with some remaining nitrile oxide precursor (tlc). The reaction mixture was therefore treated with further portions of the reactants to achieve complete consumption of the starting material. Preparative thin layer chromatography facilitated complete separation of the isomeric isoxazolines **(46a)** and **(46b)** in a combined yield of 59% and an isomer ratio of 55:45.

This result demonstrates that 2-phenyl-4,5-dihydro-oxazoline-4-carbonitrile oxide **(41)** must be generated at a low concentrations to obtain reasonable yields of oxazoline/isoxazoline cycloadducts. The fact



RS/SR

(45a)

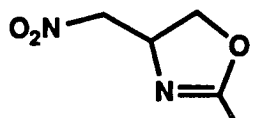


RR/SS

(45b)

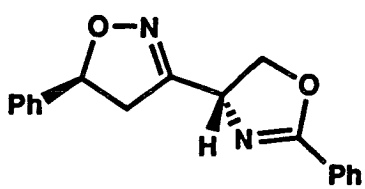
52%

Path A
p-ClC_6H_4NCO,
Et_3N, toluene,
styrene.



(42)

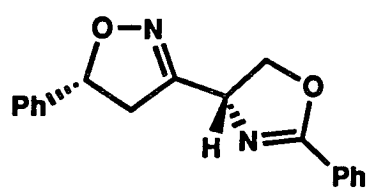
Path B
Tolylene 2,4-di-isocyanate,
Et_3N, 1,2-dichloroethane,
styrene.



RS/SR

(46a)

59%

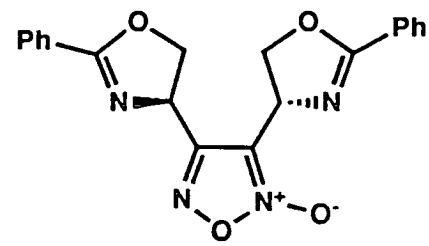


RR/SS

(46b)

Only one enantiomer of each compound is shown

scheme 47



(45b)

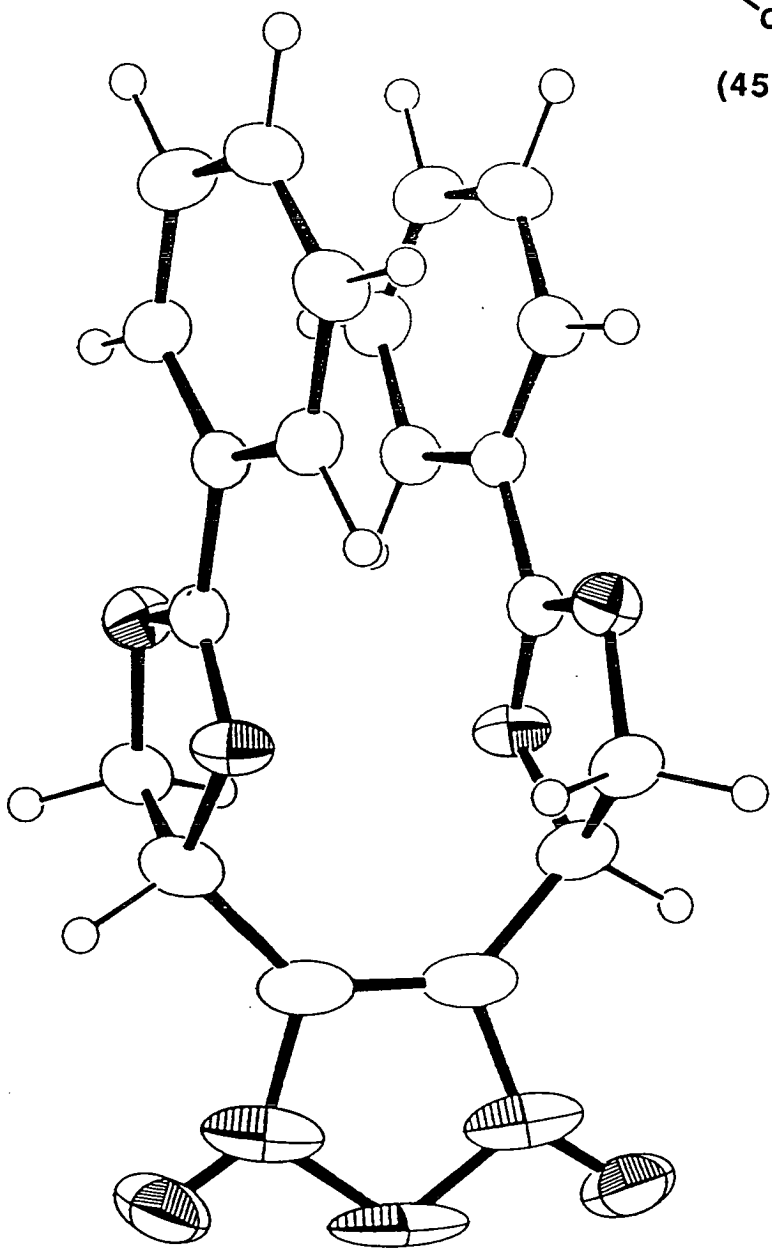


Fig. 31

that **(41)** is prone to dimerisation is consistent with it being an electron deficient nitrile oxide, which are well documented[113 114] to be prone to this reaction.

The configurations of the isoxazolines **(46a)** and **(46b)** were assigned by obtaining a single crystal *X*-ray structure (Fig. 32) on the first eluted "major" isomer. This identified it as (*RS/SR*)-5-phenyl-3-(2-phenyl-4,5-dihydro-oxazol-4-yl)-2-isoxazoline **(46a)**; thus the slower eluting adduct possesses the (*RR/SS*) configuration.

When the same procedure was applied to the cycloaddition of the nitrile oxide with oct-1-ene (scheme 48) the two diastereomeric cycloadducts (*RR/SS*)- and (*RS/SR*)-5-hexyl-3-(2-phenyl-4,5-dihydro-oxazol-4-yl)-2-isoxazoline **(47a)** and **(47b)**, were isolated in a combined yield of 77%. However, both isomers proved to be impure; subsequent purification proved difficult and costly in products and as a result no exact isomer ratio was obtained. However, based on the result of the cycloaddition reaction with styrene, and literature precedent,[74-76] it would have been expected to be approximately 1:1. The lack of any π-facial selectivity in the cycloaddition reactions of chiral nitrile oxides with achiral olefins can be attributed to the remoteness of the forming asymmetric centre from the existing one.[75]

The configurations of the products from the cycloaddition reaction with oct-1-ene were tentatively assigned on the basis of the *X*-ray structure obtained on the styrene adducts, and are based purely on the order of elution. Thus the first eluted isomer is assigned as the (*RR/SS*)-adduct **(47a)**, the slower eluting component is then the (*RS/SR*)-bis-heterocycle **(47b)**. The apparent reversal of stereochemistry is the result of the change in priority of the 5-substituent (phenyl-priority two; hexyl-priority three).

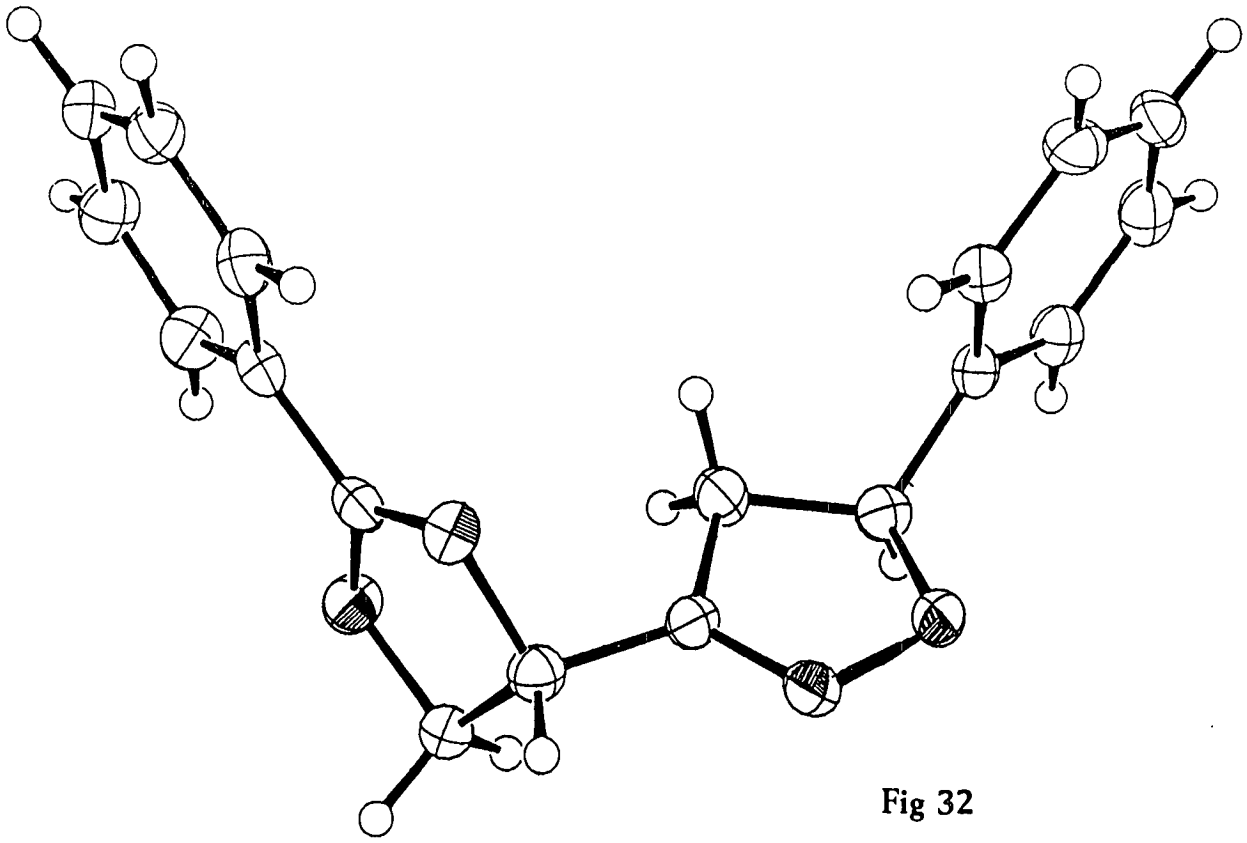
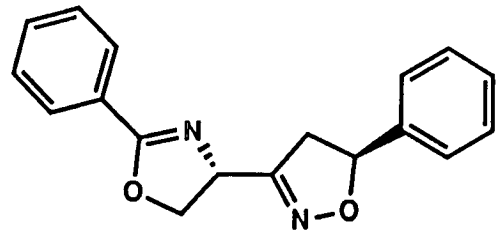
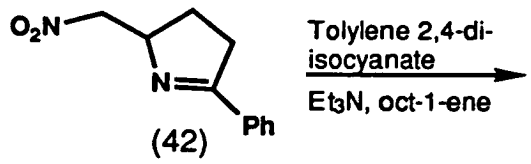


Fig 32



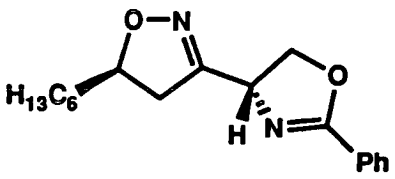
(46a)



(42)

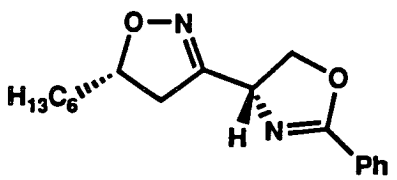
Tolylene 2,4-di-isocyanate

Et_3N, oct-1-ene



RR/SS

(47a)



SR/RS

(47b)

Only one enantiomer of each compound is shown

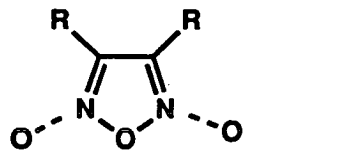
scheme 48

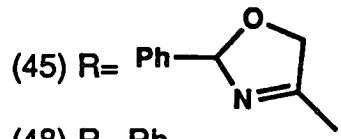
2.2.5. Features of (*RS/SR*)-5-phenyl-3-(2-phenyl-4,5-dihydro-oxazol-4-yl)-2-isoxazoline (46a) From the *X*-ray Crystal Structure.

The single crystal *X*-ray structure (Fig 32) of the faster eluting styrene cycloadduct showed it to have the (*RS/SR*) configuration. The torsion angle between the two heterocyclic rings is approximately 55°, the two ring nitrogens are arranged in a "*trans*" conformation with respect to each other. Both of the heterocyclic rings are relatively flat; the isoxazoline ring and its 5-phenyl substituent lie at an approximate angle of 60° to each other, while the oxazoline ring and its 2-phenyl substituent have a torsion angle of around 10°. This tendency towards co-planarity presumably allows the molecule to profit from the extended conjugation of the 2-phenyl group with the C=N bond of the oxazoline ring.

2.2.6 Features of (*RR/SS*)-3,4-di-(2-phenyl-4,5-dihydro-oxazol-4-yl)furazan-*N*-oxide (45b) From the *X*-ray Crystal Structure.

The *X*-ray crystal structure of **(45b)** (Fig 31) shows some disorder in the region of the furazan ring; this phenomenon is well documented in the literature.[123-125] For example it is reported that in the crystalline state there are two forms of 3,4-diphenylfurazan-*N*-oxide[124] **(48)** (Fig. 33) which were differentiated by the different torsion angles between the planes of the phenyl and heterocyclic rings.





(48) R= Ph

Fig. 33

In the present case the *X*-ray structure (Fig. 31) is not sufficiently well resolved to distinguish the two forms, and as a result an exocyclic oxygen appears on each of the nitrogen atoms of the furazan ring. The large ellipsoids which represent the three furazan heteroatoms are symptomatic of the disorder in this region of the molecule. Another feature of the crystal structure is the parallel alignment of the 2-phenyloxazoline substituents, with the heterocyclic rings arranged to accomodate the H_4 ring hydrogens.

2.2.7. Cycloaddition Reactions of (4*R*)-3-(*N*-*t*-butoxycarbonyl)-2,2-dimethyl-4-carbonitrile oxide (39).

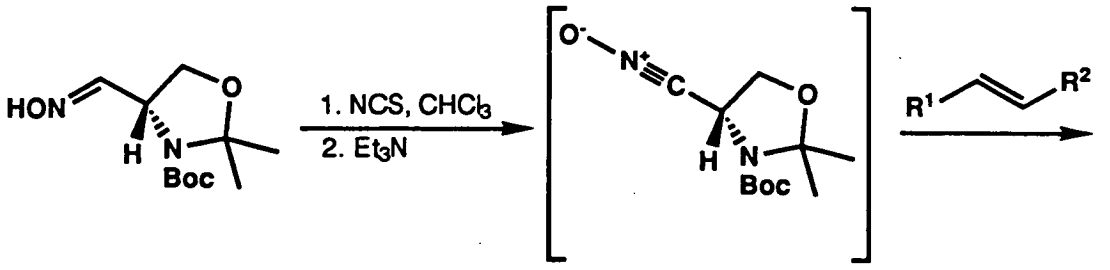
The nitrile oxide precursor (4*R*)-4-aldoximino-3-(*N*-*t*-butoxycarbonyl)-2,2-dimethyloxazolidine **(40)** was converted to the title nitrile oxide **(39)** by the procedure developed by Torssell,[40] i.e. by treatment of the oxime with NCS in chloroform followed by addition of the dipolarophile and then slowly adding a chloroform solution of triethylamine. Three alkenes were used in cycloaddition reactions with this nitrile oxide: styrene, oct-1-ene and diethyl fumarate. The results of these reactions are summarised in scheme 49.

Nitrile oxide **(39)** reacted with styrene affording the cycloadducts **(49a)** and **(49b)** in a combined yield of 65%. The isomer ratio was determined to be 59:41 after chromatographic separation of the diastereomeric products.

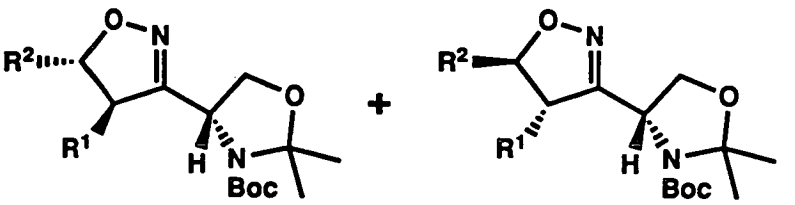
The same procedure applied to the reaction of **(39)** wth oct-1-ene furnished the two diastereomeric cycloadducts **(50a)** and **(50b)** in a ratio of 48:52 determined after separation by flash column chromatography; the combined yield was 70%.

Diethyl fumarate reacted with **(39)** giving a mixture of diastereomeric cycloadducts (36%) after chromatography. The isomeric isoxazolines **(51a)** and **(51b)** could not be completely separated; however, partial resolution was achieved by flash column chromatography thus allowing the adducts to be characterised independently.

An estimate of the diastereomer ratio was obtained for the adducts of diethylfumarate **(51a)** and **(51b)** from an expansion of the ^{1}H-NMR spectrum (200MHz) of the reaction mixture, by measuring the integrals of the two isoxazoline H_5 doublets. The isomer ratio was estimated to be *ca.* 1:1.



(40) (39)



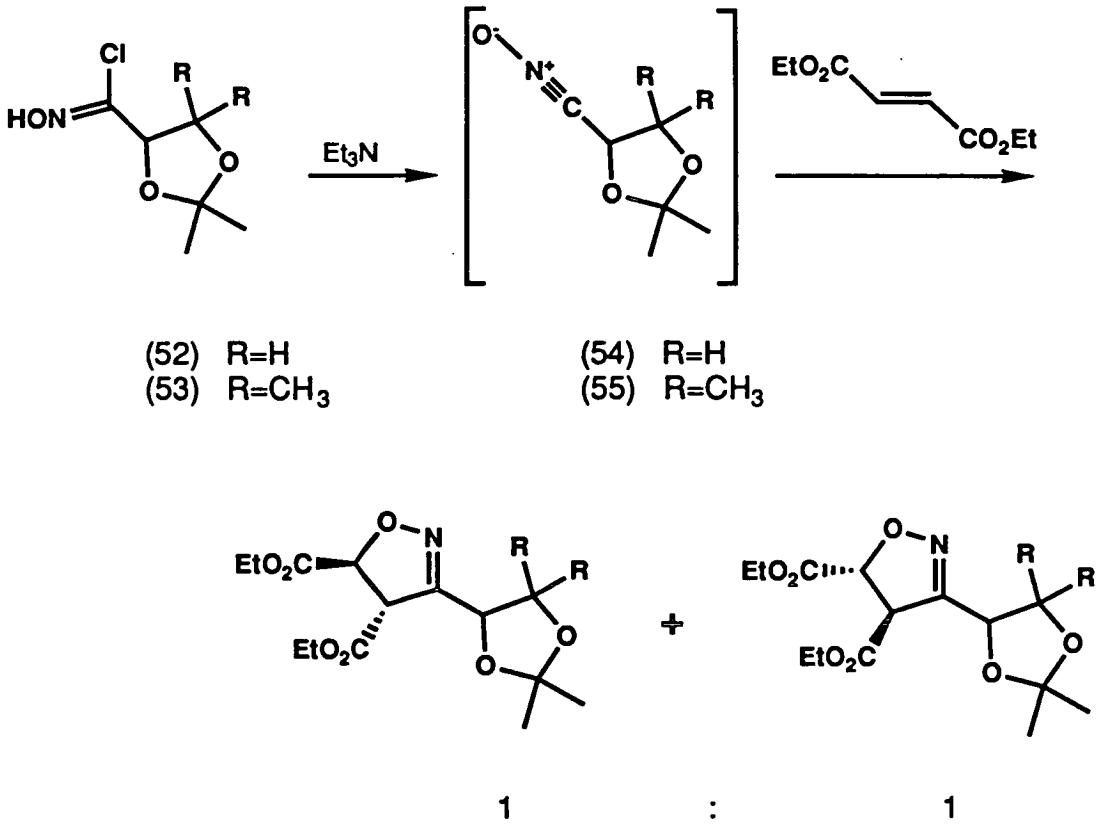
R^1=H, R^2=Ph	(5*R*,4'*R*)	R^1=H, R^2=Ph (5*S*,4'*R*)
R^1=H, R^2=C_6H_{13}	(5*S*,4'*R*)	R^1=H, R^2=C_6H_{13} (5*R*,4'*R*)

	Yield (%)					
R^1=H, R^2=Ph	65	(49a)	59[a]	:	(49b)	41
R^1=H, R^2=C_6H_{13}	70	(50a)	48[a]	:	(50b)	52
R^1=R^2=CO_2Et	36	(51a)	53[bc]	:	(51b)	47

a. ratio of isolated products
b. estimated from ^{1}H-NMR of reaction mixture
c. arbitrary assignment of stereochemistry

scheme 49

Thomas and co-workers[75] found that the cycloadditions of nitrile oxides **(54)** and **(55)** (Scheme 50), generated from the corresponding hydroximoyl chlorides **(52)** and **(53)**, with diethyl fumarate also afforded a 1:1 mixture of cycloadducts in both cases.



scheme 50

The ^{1}H-NMR spectra of the cycloadducts of the oxazolidine nitrile oxide **(39)** at room temperature show poor resolution of some signals; but when the spectra are re-run at approximately 60°C there is a distinct improvement in the resolution. This is exemplified in Fig. 34 with the spectrum of **(49b)** recorded at both temperatures. This is again attributed to "flipping" between the different conformations of the oxazolidine ring, which at room temperature may be slow enough to cause broadening of the signals. This has previously been reported by Garner and Park[101] to occur with the oxazolidine methyl ester **(17)** and by Mann and co-workers[105] for a similar 4-substituted system **(56)**.

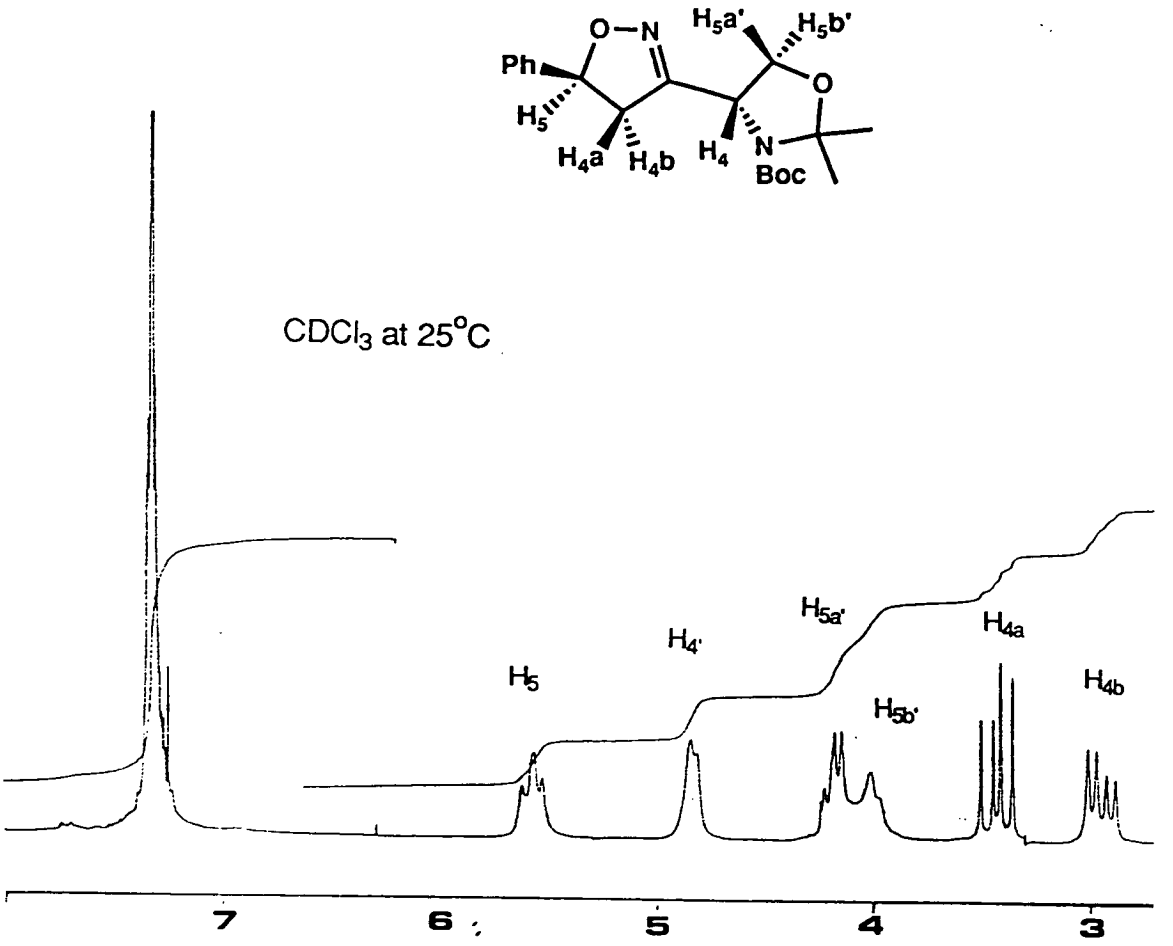
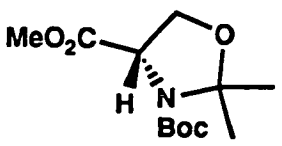
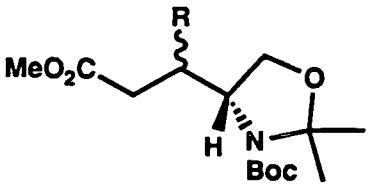

Ph
H5
H4a
H4b
H4
O—N
H5a'
H5b'
O
N
Boc
CDCl3 at 25°C
H5
H4'
H5a'
H5b'
H4a
H4b
7
6
5
4
3
CDCl3 at 60°C
H5
H4'
H5a'
H5b'
H4a
H4b
7
6
5
ppm
4
3

Fig 34



(17)



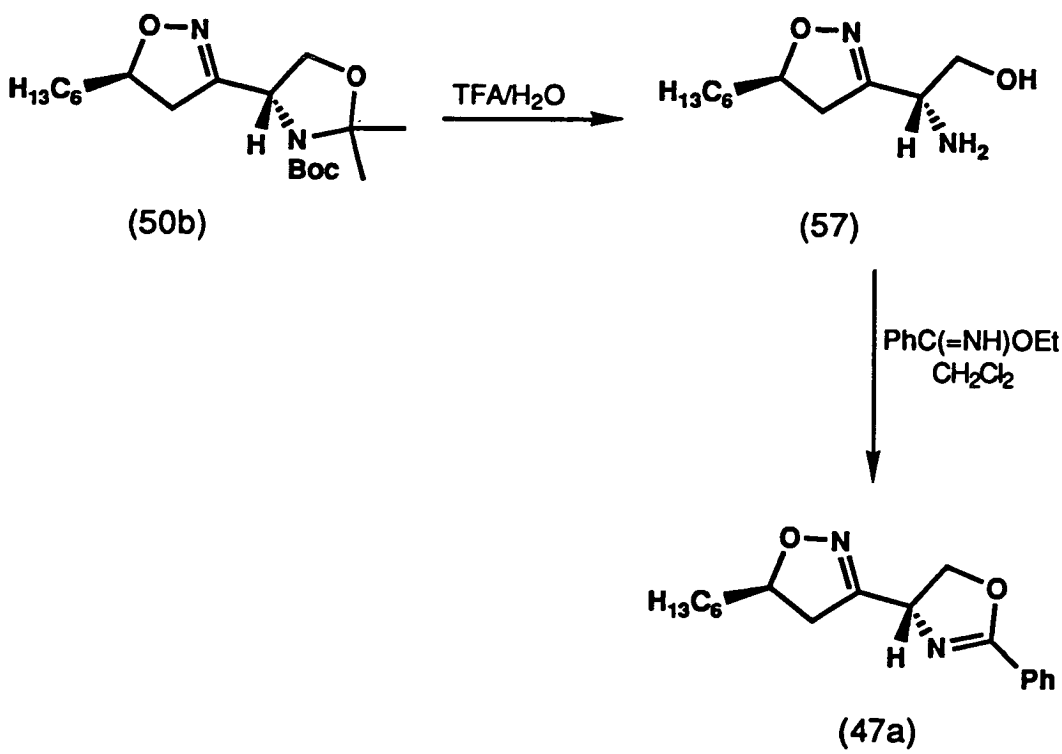
(56)

2.2.8 Assignment of Configuration.

It was not possible to grow crystals for *X*-ray analysis. Instead it was decided that an attempt could be made to assign the configurations by relating the oxazolidine/isoxazoline adducts to the products of the cycloaddition reactions of 2-phenyl-4,5-dihydro-oxazole-4-carbonitrile oxide (**41**). These had been assigned on the basis of a single crystal *X*-ray structure obtained on the faster eluting adduct of styrene, (*RS/SR*)-5-phenyl-3-(2-phenyl-4,5-dihydro-oxazol-4-yl)-2-isoxazoline (**46a**). To this end cycloadduct (**50b**), the slower eluting isomer from the reaction between nitrile oxide (**39**) and oct-1-ene, was treated with trifluoroacetic acid and water at room temperature, thus completely deprotecting the amino-alcohol moiety. The product was isolated in 63% yield (scheme 51) after flash chromatography. This compound (**57**) proved to be unstable at room temperature, it was therefore characterised by ^{1}H-NMR (all the signals were broad and poorly resolved) and an accurate FAB mass spectrum. It was then reacted with ethyl benzimidate in dichloromethane, furnishing, after preparative thin layer chromatography, oxazoline (**47a**) in 44% yield ($[\alpha]_D$ (21°C) +24.5° (c 0.1 in $CHCl_3$).

Comparison of the ^{1}H-NMR spectrum of (**47a**) with the spectra of the adducts (**47a**) and (**47b**), formed in the reaction of 2-phenyl-4,5-

dihydro-oxazole-4-carbonitrile oxide **(41)** and oct-1-ene, show it to correspond to the first eluted isomer from that reaction. This has been tentatively assigned the (*RR/SS*) configuration. On this basis the first eluted cycloadduct from the cycloaddition reaction of oct-1-ene with (4*R*)-3-(*N*-*t*-butoxycarbonyl)-2,2-dimethyloxazolidine-4-carbonitrile oxide **(39)** is (5*S*,4'*R*)-5-hexyl-3-[3'-(*N*-*t*-butoxycarbonyl)-2',2'-dimethyloxazolidin-4'-yl]-2-isoxazoline **(50a)**, while the slower eluting isomer **(50b)** possesses the (5*R*,4'*R*) configuration. Extrapolating this to the adducts formed between the oxazolidine-nitrile oxide **(39)** and styrene, the diastereomer which eluted first was assigned as (5*R*,4'*R*)-5-phenyl-3-[3'-(*N*-*t*-butoxycarbonyl)-2',2'-dimethyloxazolidin-4'-yl]-2-isoxazoline **(49a)**, while the second eluted isomer **(49b)** was assigned the (5*S*,4'*R*) configuration.

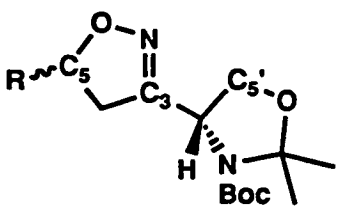


(50b) (57) (47a)

scheme 51

The relationship between the oxazolidine nitrile oxide **(39)** cycloadducts with styrene and oct-1-ene was not made purely on the order of elution; while the ^{1}H-NMR spectra of the isomeric pairs are virtually identical, there were some differences in the ^{13}C-NMR which were consistent for both sets of compounds, these are shown in Fig. 35. For the three carbon atoms shown the slower eluting isomer of each pair of compounds have their signals at slightly higher chemical shift.

No attempt has been made to assign the absolute configuration of the cycloadducts of nitrile oxide **(39)** with diethyl fumarate.



	(49a)	(49b)	(50a)	(50b)
C_3	157.8	158.2	158.3	158.5
C_5	81.8	81.9	80.85	81.0
$C_{5'}$	66.3	66.7	66.6	66.8

Chemical shift (ppm) in $CDCl_3$

Fig. 35

2.2.9. Final Comments on the ^{1}H-NMR Spectra of the Chiral Nitrile Oxide Adducts.

In the ^{1}H-NMR spectra of several of these cycloadducts the signals for each of the isoxazoline H_{4a} and H_{4b} resonances show fine splitting (*ca.* 0.8 Hz). This is attributed to long range (^4J) coupling with the $H_{4'}$ hydrogen of the oxazolidine and oxazoline rings. This hypothesis was confirmed by a decoupling experiment in which the oxazoline $H_{4'}$ proton

of (*RR/SS*)-5-phenyl-3-(2-phenyl-4,5-dihydro-oxazol-4-yl)-2-isoxazoline **(46b)** was irradiated; this resulted in the collapse of the fine splitting of the isoxazoline H_4 signals (Fig. 36).

2.2.10. Conclusion.

The cycloaddition reactions of the two heterocyclic nitrile oxides **(39)** and **(41)** furnished the corresponding bis-heterocyclic adducts in poor to moderate yield. When the oxazoline-nitrile oxide **(41)** was not formed in a low steady state concentration only the furoxans **(45a)** and **(45b)** were isolated.

In all of the cycloaddition reactions π-facial selectivity was very poor, this is consistent with previous reports.[74-76]

Removal of the β-amino-alcohol protection resulted in the formation of the 3-amino-ethanol-2-isoxazoline **(57b)**; this compound was unstable at room temperature.

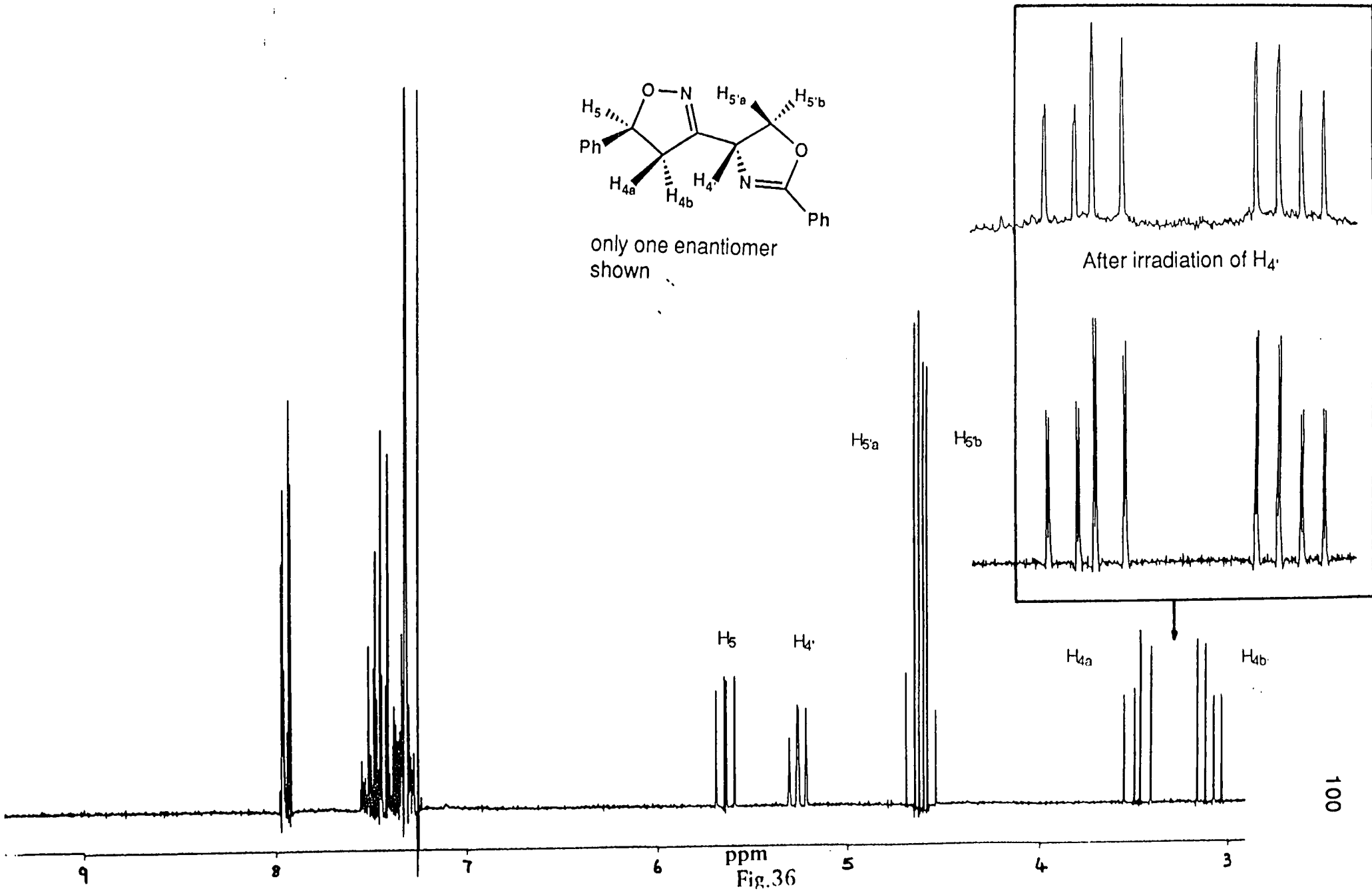
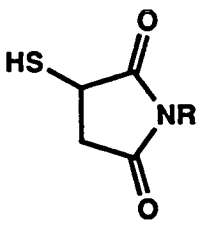

O—N
H5'a
H5'b
H5
Ph
O
H4a
H4'
N
H4b
Ph
only one enantiomer shown
After irradiation of H4'
H5'a
H5'b
H5
H4'
H4a
H4b
9
8
7
6
ppm
5
4
3

Fig.36

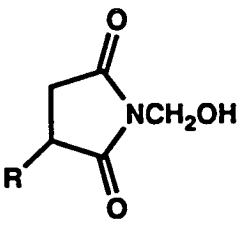
2.3. Synthesis of 3,3'-bi-isoxazoles and Lower Oxidation State Analogues *via* Isoxazole- and 2-Isoxazoline-3-carbonitrile Oxides.

2.3.1. Introduction.

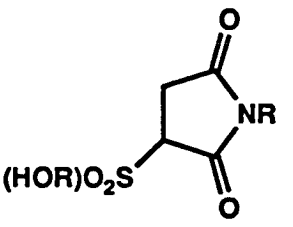
There are many examples of nitrogen and oxygen containing heterocyclic compounds in the patent literature which function as lubricant additives.[126] These are exemplified by the structures shown in Fig. 37 which have been patented as friction modifiers.



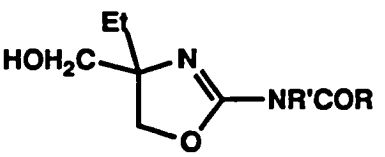
R=12-22C alkyl



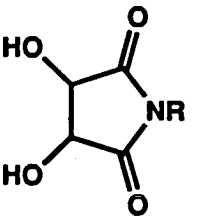
R groups not defined in survey



R=10-36C aliphatic



R and R' not defined in survey



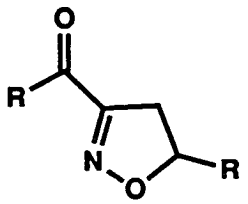
eg *N*-octyltartaramide

Fig 37

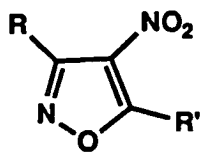
Friction modifiers are usually oil soluble long chain polar molecules which show a strong tendency to be adsorbed onto metal surfaces. They form ordered multi-decked layers, the outer layers of which are easily sheared off giving a low coefficient of friction.

There are also examples of isoxazoles and their saturated analogues

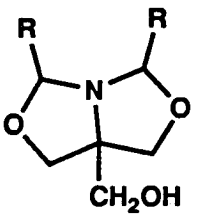
functioning as corrosion inhibitors (Fig. 38). Addition of corrosion inhibitors to hydrocarbon oils is desirable because oxidation of this type of base oil can yield a variety of compounds which attack metals and promote rust. Corrosion inhibitors can act in two ways: they can neutralise acidic products formed from oxidation of the oil, or by the formation of a corrosion resistant film on the metal surface.



R=2-20C



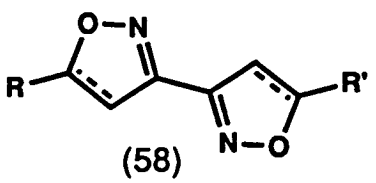
R=6-20C Aryl
R=1-20C Alkyl
R'=1-30C Alkyl



R groups not defined in survey

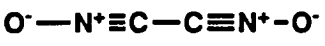
Fig. 38

The synthesis of 3,3'-bi-isoxazoles, 3,3'-isoxazolylisoxazolines and 3,3'-bi-isoxazolines might provide novel compounds which could be of interest as lubricant additives. The reason for choosing the 3,3'-bis-heterocycles (**58**), as opposed to isomers with different points of ring linkage, was that suitable precursors to the isoxazole- and isoxazoline-3-carbonitrile oxides were readily available, and that a planar arrangement of the resulting cycloadduct's two heterocyclic rings, with respect to each other, would be predicted on the basis of extended conjugation involving the C=N double bonds. This may enhance adsorption at a metal surface.



(58)

Previous approaches to 3,3'-bi-isoxazoles and isoxazolines have involved the use of either oxalodinitrile oxide **(59)** or isoxazole- and isoxazoline-3-carbonitrile oxides. There follows a brief survey of the relevant literature.

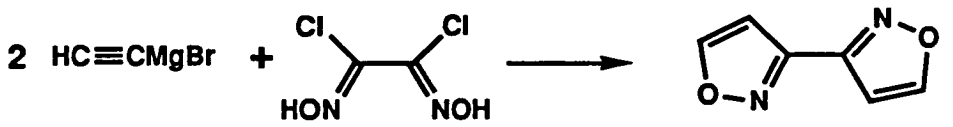


(59)

2.3.1.1. Use of Oxalodinitrile Oxide in the Synthesis of 3,3'-bi-isoxazoles.

Oxalodinitrile oxide (dicyanogen-bis-*N*-oxide) cycloadditions with olefins and acetylenes provide the most obvious approach to this class of bis-heterocycle and, although this nitrile oxide is known to be explosive,[127] the dangers are minimised by *in situ* generation. A significant synthetic limitation of this procedure, however, is that non-symmetrical 3,3'-bi-isoxazoles cannot be readily prepared.

The parent member of the 3,3'-bi-isoxazole series **(62)** was first prepared by Quilico and co-workers[128] in 1957 (scheme 52) by the cycloaddition of oxalodinitrile oxide **(59)**, generated from dichloroglyoxime **(61)**, with ethynylmagnesium bromide **(60)**.

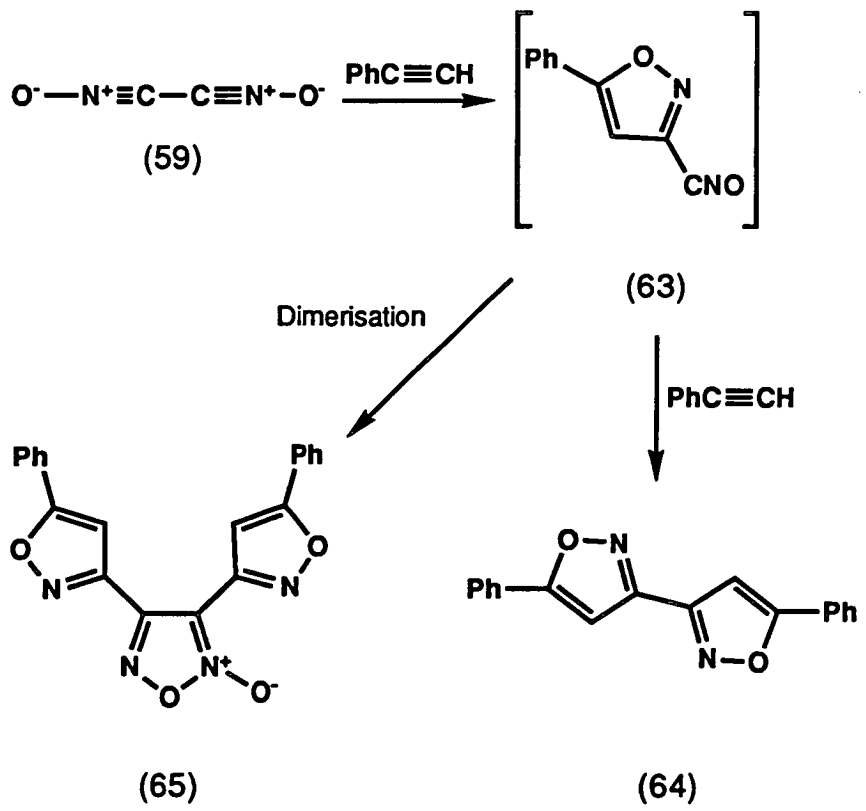


(60) (61) (62)

scheme 52

Grundmann[129] carried out an extensive investigation of the reactions of oxalodinitrile oxide, including 1,3-dipolar cycloaddition reactions with phenylacetylene, diphenylacetylene, styrene, maleic anhydride, *trans*-stilbene, cyclohexadiene, cyclopentadiene, and butadiene.

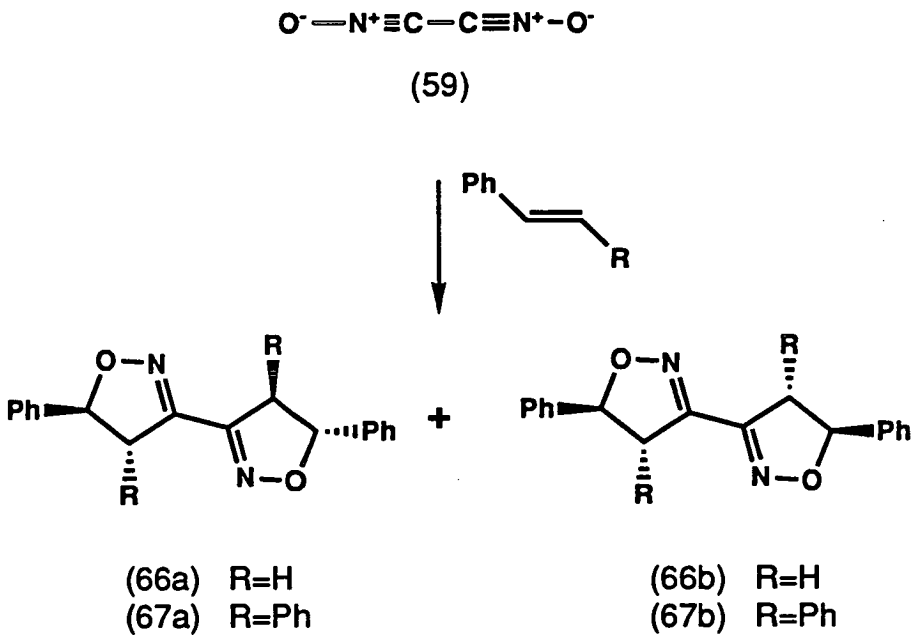
The reaction with phenylacetylene afforded an 80% yield of 5,5'-diphenyl-3,3'-bi-isoxazole **(64)** along with 15% of 3,4-bis-(5-phenylisoxazol-3-yl)furoxan **(65)** which results from dimerisation of the intermediate isoxazole-3-carbonitrile oxide **(63)** (scheme 53).



scheme 53

The corresponding reaction with diphenylacetylene was reported to have produced no cycloadducts due to the low reactivity of the dipolarophile. The cycloaddition to styrene furnished a mixture of diastereomers, "*cis*-" and "*trans*-"bi-isoxazolines **(66a)** and **(66b)**, in good yield (scheme 54).

The exact stereochemistry of each of the adducts was not established. **(59)** also reacted with *trans*-stilbene to give a pair of diastereomeric adducts **(67a)** and **(67b)** (scheme 54).



(66a) R=H
(67a) R=Ph

(66b) R=H
(67b) R=Ph

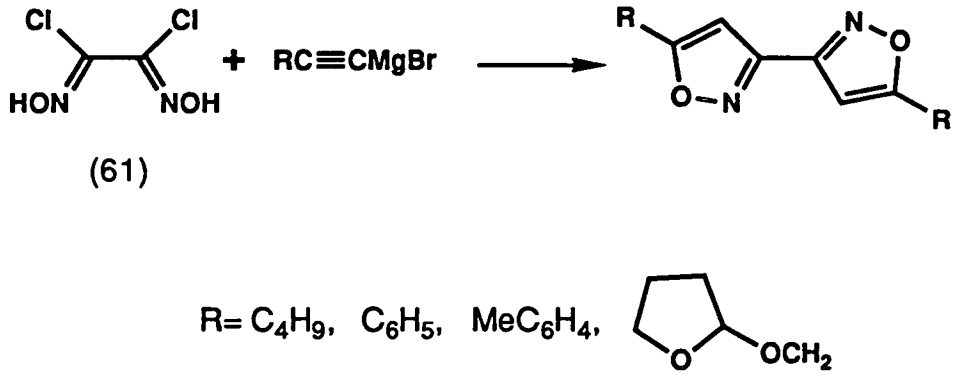
scheme 54

Other workers have also made use of oxalodinitrile oxide for the preparation of 3,3'-bi-isoxazoles and polyisoxazoles. Quilico[128] used **(59)** to prepare a series of bi-isoxazoles by reacting dichloroglyoxime **(61)** with a variety of acetylenic magnesium bromides (scheme 55).

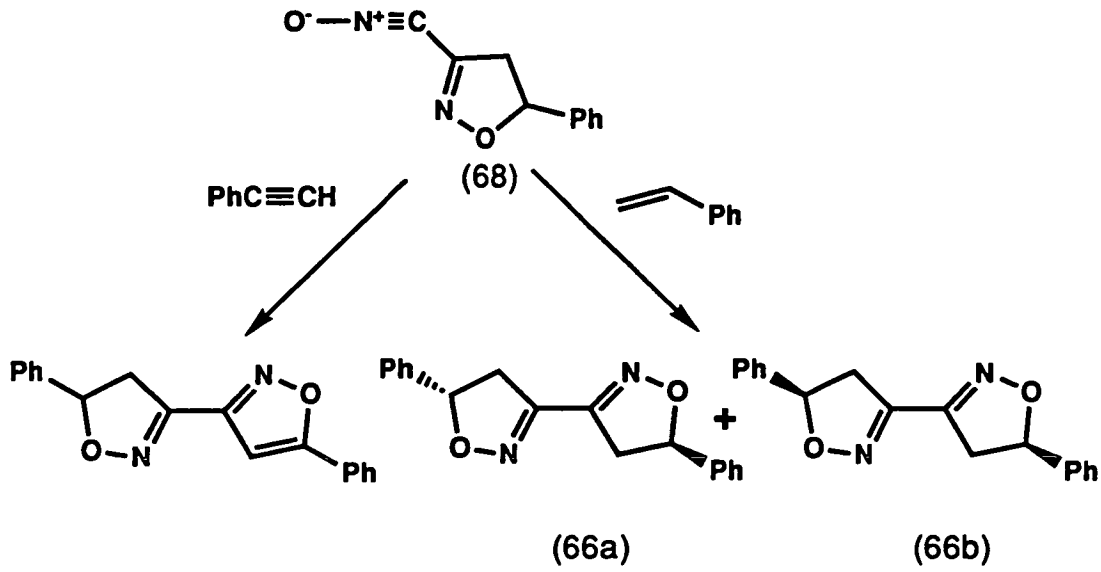
2.3.1.2. Use of Isoxazole- and 2-Isoxazoline-3-hydroximoyl Halides.

One of the attractive features of using the heterocyclic hydroximoyl halides for the preparation of bi-isoxazoles is that non-symmetrical products can be obtained. In 1965, the cycloaddition reaction of 5-phenyl-2-isoxazoline-3-carbonitrile oxide **(68)**, generated by thermal elimination of hydrogen chloride from the corresponding hydroximoyl

chloride in refluxing toluene, with styrene,[130] afforded bi-isoxazolines **(66a)** and **(66b)** identical to those prepared from oxalodinitrile oxide[129] (scheme 56). The same nitrile oxide is also reported to have been reacted with phenylacetylene. Oxidation of the isoxazoline rings of **(66a)** and **(66b)** furnished the corresponding bi-isoxazoles.



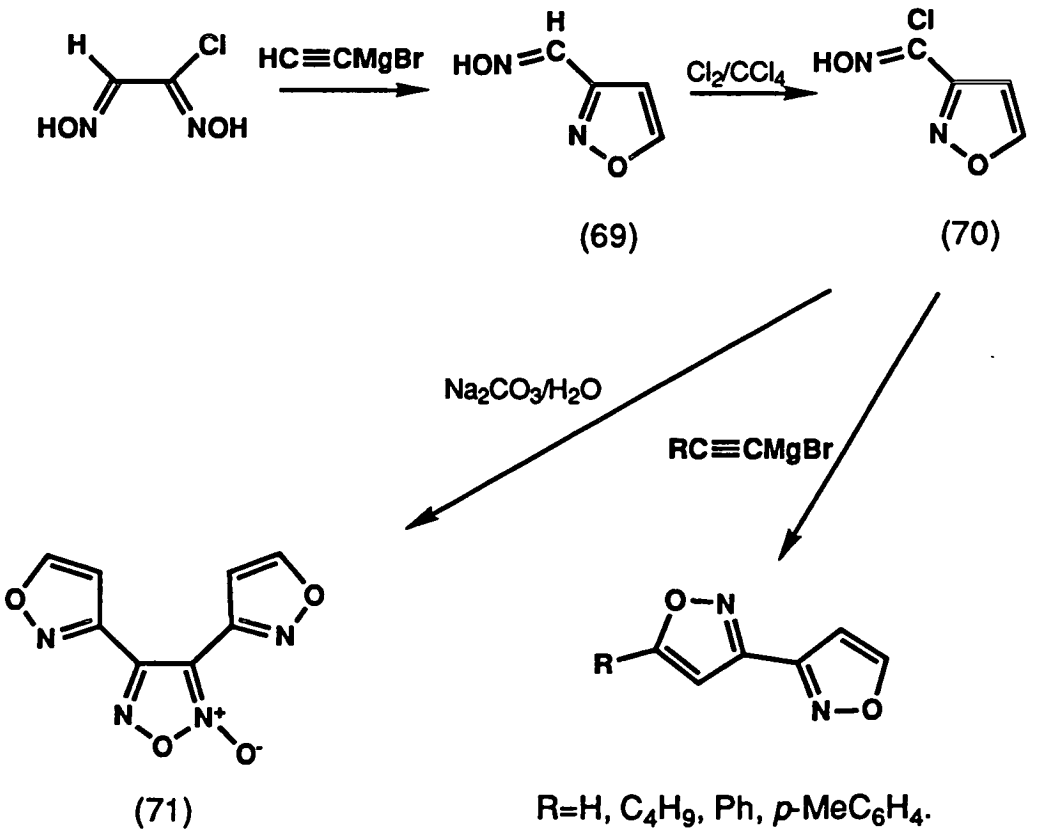
scheme 55



scheme 56

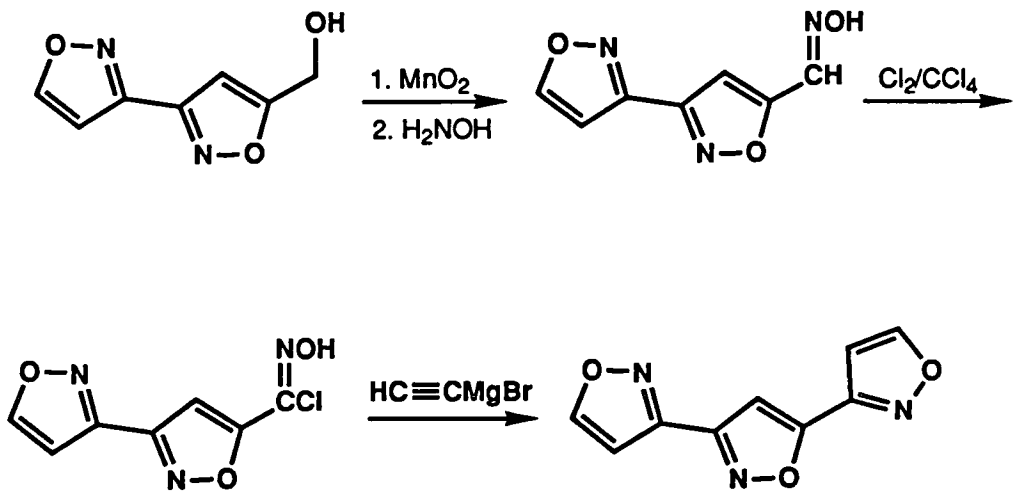
There are also some examples in the literature of the use of isoxazole-3-hydroximoyl chlorides as nitrile oxide precursors in the synthesis of bi-isoxazoles[131] and polyisoxazoles.[132 133]

Ricca and Gaudiano[131] prepared isoxazole-3-hydroximoyl chloride **(70)** by reaction of β-chloroglyoxime with ethynylmagnesium bromide, which afforded 3-aldoximinoisoxazole **(69)**, followed by treatment with chlorine gas in carbon tetrachloride (scheme 57). The hydroximoyl chloride **(70)** was reported to be very irritating to the mucous membranes. Dehydrochlorination of **(70)** in the absence of a dipolarophile yielded the furoxan **(71)**, while reaction with acetylenic magnesium bromides furnished a range of 3,3'-bi-isoxazoles in yields which varied from 20-57%.



scheme 57

The same approach, namely the addition of hydroximoyl chlorides to acetylenic magnesium bromides, has been applied to the preparation of polyisoxazoles containing three, four and six rings.[132 133] 3,3',5',3''-tri-isoxazole (**72**) was synthesised in four steps and 43% overall yield by the sequence of reactions depicted in scheme 58.

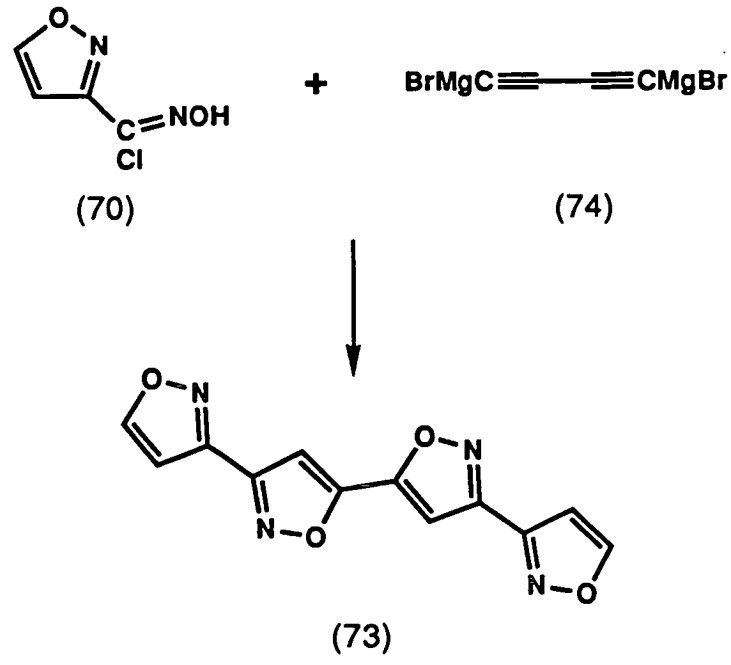


(72)

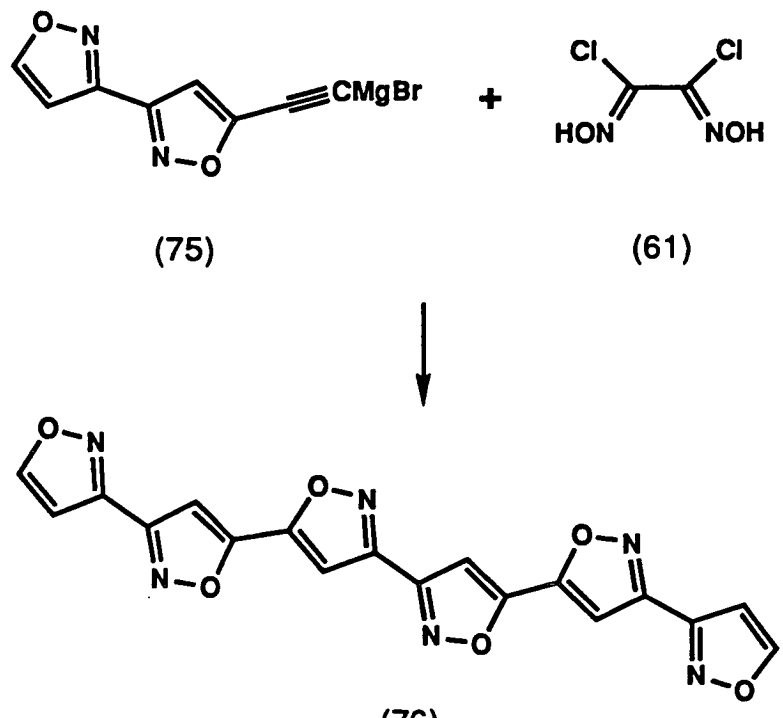
scheme 58

The tetraisoxazole member of the series (**73**) was prepared by the reaction of an excess of isoxazole-3-hydroximoyl chloride (**70**) with butadiynyldimagnesium bromide (**74**) in 47% yield (scheme 59).

The largest analogue 3,3',5',5'',3'',3''',5''',5'''',3'''',3'''''-hexaisoxazole (**76**) was prepared in 40% yield by reaction of dichloroglyoxime (**61**) with an excess of 3,3'-bi-isoxazolyl-5-ethynylmagnesium bromide (**75**) (scheme 60).



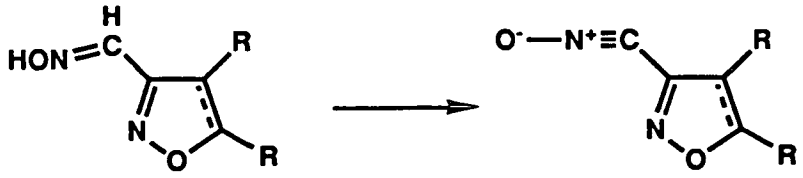
scheme 59



scheme 60

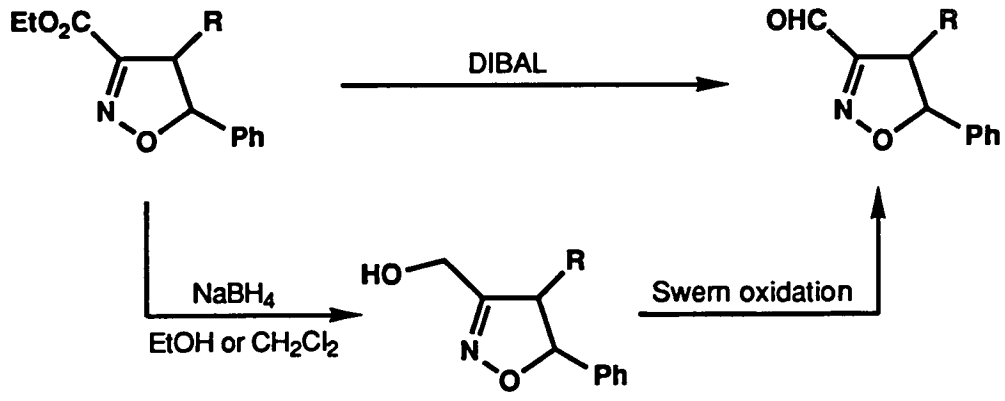
2.3.2. Preparation of Substituted Isoxazole- and 2-Isoxazoline-3-aldoximes.

In the present work isoxazole- and isoxazoline-3-aldoximes were seen as convenient precursors to the desired heterocyclic-3-carbonitrile oxides (scheme 61), as they could be prepared in three steps from readily available starting materials, namely ethyl chloro-oximidoacetate, which is in turn readily accessible from glycine ethyl ester hydrochloride.



scheme 61

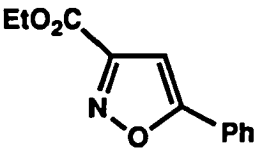
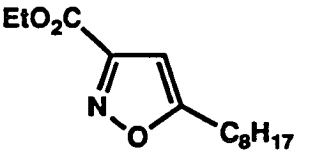
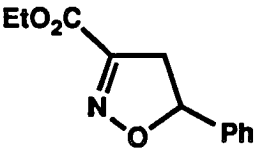
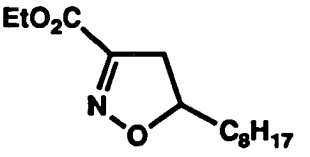
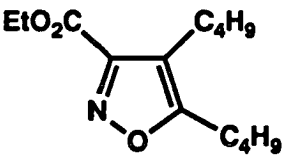
The synthetic sequence relies heavily on the methodology developed by Wade and De Micheli[134] for the conversion of 3-ethoxycarbonyl-2-isoxazolines to the corresponding 3-formyl-2-isoxazolines either by direct hydride reduction (DIBAL) or by reduction to the methyl alcohol followed by oxidation to the aldehyde (scheme 62).



scheme 62

Ethyl chloro-oximidoacetate was prepared in good yield according to the literature procedure[135] and used in the subsequent preparation of 5-substituted isoxazoles and isoxazolines **(77a-e)** (table 6).

Table 6. Cycloaddition reactions with ethoxycarbonylformonitrile oxide

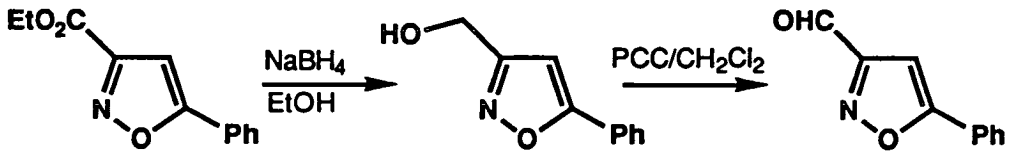
Dipolarophile	Adduct	No.	Yield (%)	Procedure
$PhC{\equiv}CH$		77a	70	A
$H_{17}C_8C{\equiv}CH$		77b	79	B
$PhCH{=}CH_2$		77c	91	B
$H_{17}C_8CH{=}CH_2$		77d	100	B
$H_9C_4C{\equiv}CC_4H_9$		77e	31	A

A. Nitrile oxide generated by thermal elimination of HCl in refluxing xylene.
B. Nitrile oxide generated by treatment with triethylamine.

In the cycloaddition reactions of ethoxycarbonylformonitrile oxide with phenyl acetylene **(77a)** and dec-5-yne **(77e)**, the 1,3-dipole was generated by thermal dehydrochlorination[49-51] of ethyl chloro-oximidoacetate in refluxing xylene, due to the lower reactivity of these

dipolarophiles. The reactions with dec-1-yne (**77b**), styrene (**77c**) and dec-1-ene (**77d**) were carried out using the slow addition of triethylamine *via* a syringe pump to generate the nitrile oxide.

The first attempt to convert 3-ethoxycarbonyl-5-phenylisoxazole (**77a**) to the corresponding 3-formylisoxazole (**79a**) involved reduction of the ester to the 3-methylalcohol (**78**) followed by oxidation to the aldehyde (scheme 63). The reduction with sodium borohydride proceeded in high yield (86%); the oxidation to the aldehyde (**79a**) (82%) was effected using pyridinium chlorochromate (PCC).[111] In the procedure developed by Wade *et al*[134] the latter oxidative transformation was made under Swern oxidation conditions;[112] however, it was felt that PCC oxidation was a more straightforward protocol as it does not require the drying of several reagents, including DMSO, beforehand.



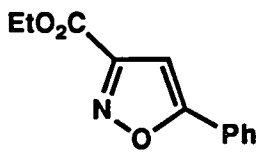
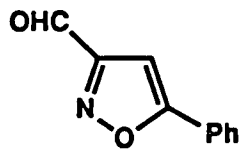
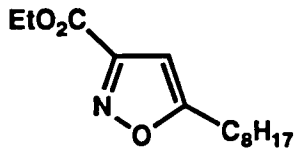
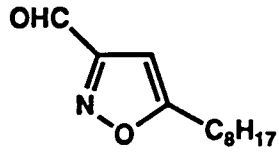
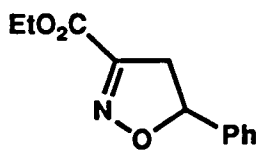
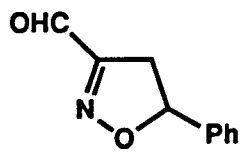
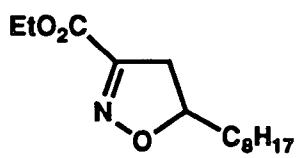
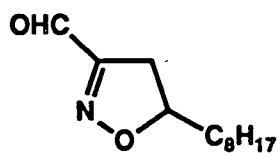
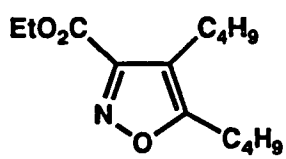
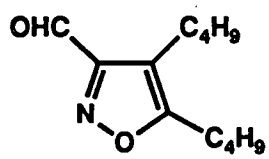
(77a) (78) (79a)

scheme 63

The second and more direct approach developed by Wade and co-workers[134] involved direct conversion of the ester to the aldehyde by reduction with DIBAL. When the same procedure was applied to the conversion of the ester (**77a**) to aldehyde (**79a**) the latter was isolated in 85% yield, as a sweet-smelling white powder. A small amount (13%) of alcohol (**78**) was also isolated in this reaction. Having tested the methodology on ester (**77a**), the one step reductive method (DIBAL) was adopted for the conversion of esters (**77a-e**) to the corresponding

aldehydes (**79a-e**). The results are shown in table 7.

Table 7. DIBAL reduction of esters 77a-e.

	Ester (77)	Aldehyde (79)	Yield (%)
a			85
b			87
c			51
d			73
e			83

The aldehydes (**79a-e**) were purified by flash column chromatography over silica or by Kugelrohr distillation. The lower yield of 3-formyl-5-phenyl-2-isoxazoline (**79c**), although comparable to that reported by Wade[134] (63%), is thought, at least in part, to be due to some decomposition during distillation.

Two approaches were investigated for the conversion of the isoxazole- and 2-isoxazoline-3-carboxaldehydes to their corresponding oximes: the first made use of a two phase system while the second involved pyridine as the solvent.

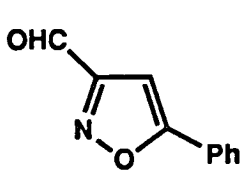
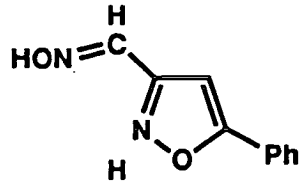
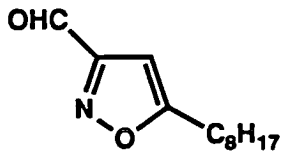
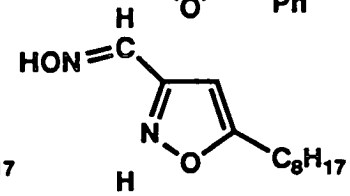
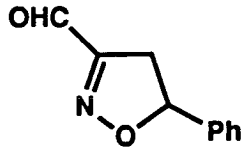
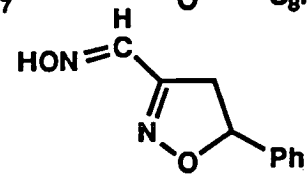
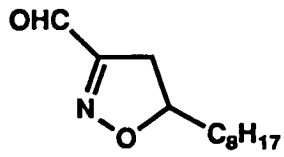
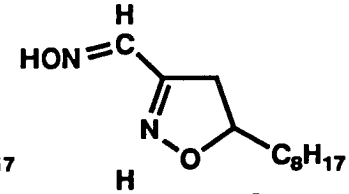
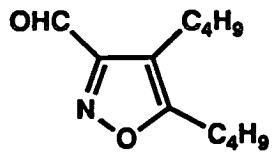
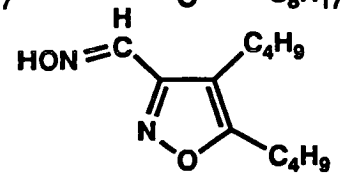
The first approach, in which the hydroxylamine hydrochloride was added to an aqueous sodium hydroxide solution followed by the addition of an ethereal solution of the aldehyde, suffered from the problem that the oxime, once formed, tended to precipitate as the sodium salt. This was overcome by adding chloroform which dissolved the salt. This procedure was tested on aldehydes **(79a)** and **(79d)** and afforded the oximes in 70% and 77% yields respectively. However, reaction times were found to be quite long and additions of further sodium hydroxide solution and hydroxylamine hydrochloride was required to achieve complete consumption of the aldehyde.

Pyridine proved to be a superior solvent for this conversion; reactions are generally complete in about one hour and yields of oxime were good to excellent (table 8).

It is interesting to note that only the 5-alkyl substituted heterocycles seem to give an appreciable amount of the *Z*-oxime, whereas the 5-phenyl substituted rings and the 4,5-disubstituted isoxazole **(80e)** give almost exclusively the *E*-oxime. However, it must be noted that in all but the case of oxime **(80d)** the oximation products were not analysed (^{1}H-NMR) until after purification and so small amounts of the *Z*-oxime may have been lost.

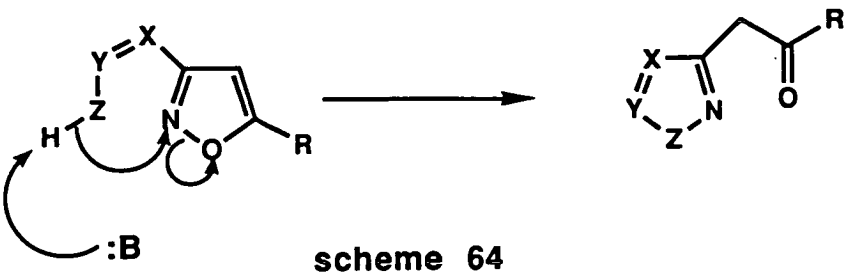
The effect on the *E/Z*-isomer ratios of the two different methodologies employed for the preparation of the oximes was investigated in the case of 3-aldoximino-5-octyl-2-isoxazoline **(80d)**. The products from both solvent systems were analysed by ^{1}H-NMR before recrystallisation; this showed that the two phase system afforded a mixture of isomers (63:37), while carrying out the reaction in pyridine resulted in almost exclusive formation of the *E*-oxime (<95%).

Table 8. Preparation of oximes 80a-e.

	Aldehyde (79)	Oxime (80)	Yield (%)	*E/Z* Ratio
a			70[a] 90[b]	*ca* 100:0[c] *ca* 100:0[c]
b			89[b]	87:13[c]
c			94[b]	*ca* 100:0[d]
d			77[a] 81[b]	63:37[e] <95%*E*[e]
e			79[b]	*ca* 100:0[c]

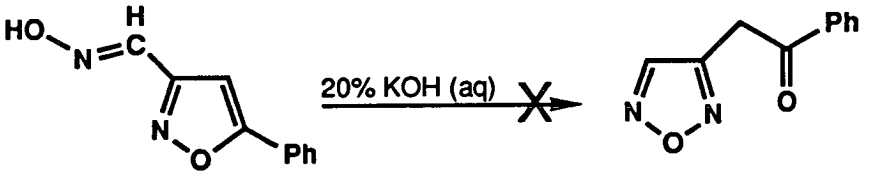
a) Two phase procedure. b) Pyridine as solvent. c) Recrystallised product. d) Distilled product. e) Crude reaction product.

The stereochemical identification of the isomers was made on the basis of the attempted rearrangement of 3-aldoximino-5-phenylisoxazole **(80a)** in the presence of base. This reaction, sometimes known as the Boulton-Katritzky rearrangement[136] (scheme 64), is believed to involve a nucleophilic displacement at nitrogen[137] and in the case of oximes has been shown only to occur with the *Z*-isomer.[136] When an ethanolic



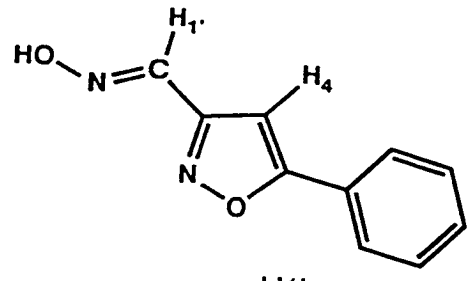
scheme 64

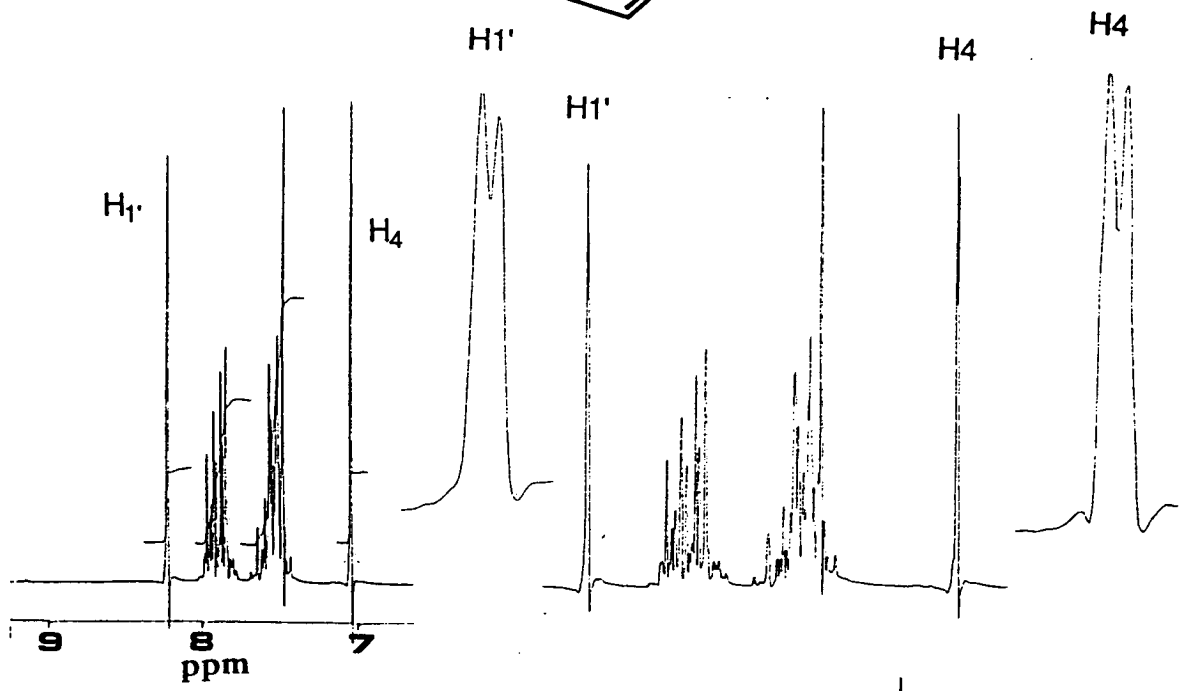
solution of **(80a)** was treated with 20% aqueous potassium hydroxide under reflux for 100 minutes, only the starting oxime was isolated. It was therefore assigned the *E*-configuration (scheme 65). The stereochemistry of the other oximes was assigned by analogy.



scheme 65

The ^{1}H-NMR spectra of both the isoxazole and 2-isoxazoline oximes **(80a-d)** show a long range coupling (^4J) between the protons at the 4-position of the ring and the oxime hydrogen (Fig. 39) (page 119). The existence of this long range coupling was confirmed by irradiation of the oxime proton of 3-aldoximino-5-phenylisoxazole **(80a)** and 3-aldoximino-5-octyl-2-isoxazoline **(80d)**; in both cases this resulted in the collapse of the fine splitting of the heterocyclic H_4 ring protons (Fig. 40 & 41). This observation is consistent with a similar long range coupling seen in the ^{1}H-NMR spectra of the adducts of 5-phenyl-4,5-dihydro-oxazole-3-carbonitrile oxide (sect 2.2.9) which was also confirmed by a ^{1}H-NMR irradiation experiment (Fig. 42).


HO
N
C
H1'
H4
N
O


H1'
H4
H4
H1'
H1'
H4
9
8
7
ppm

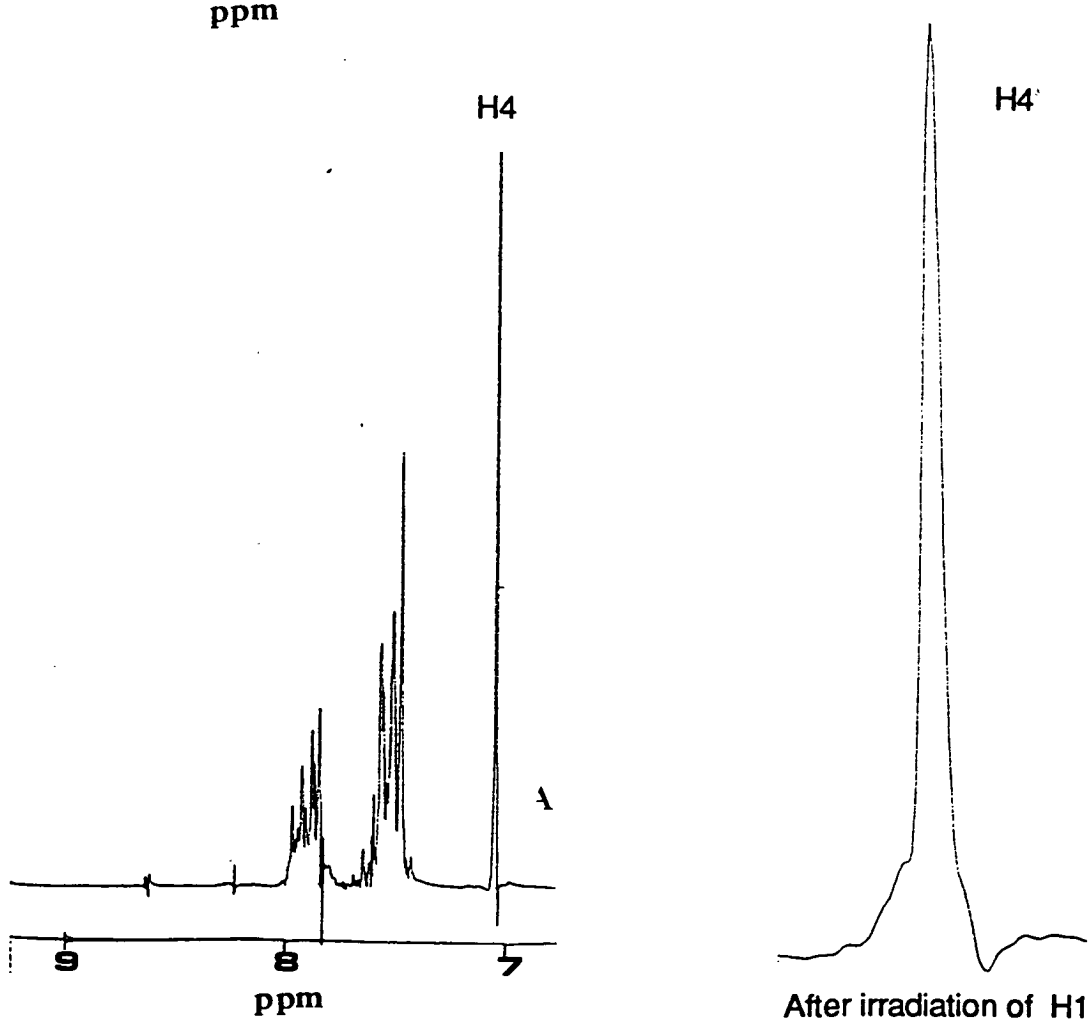
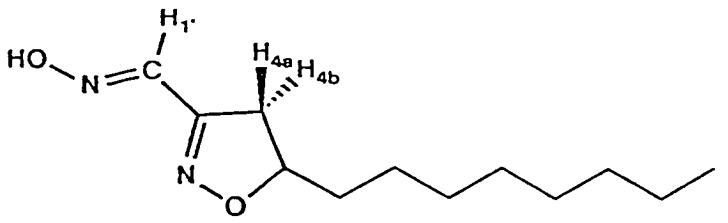
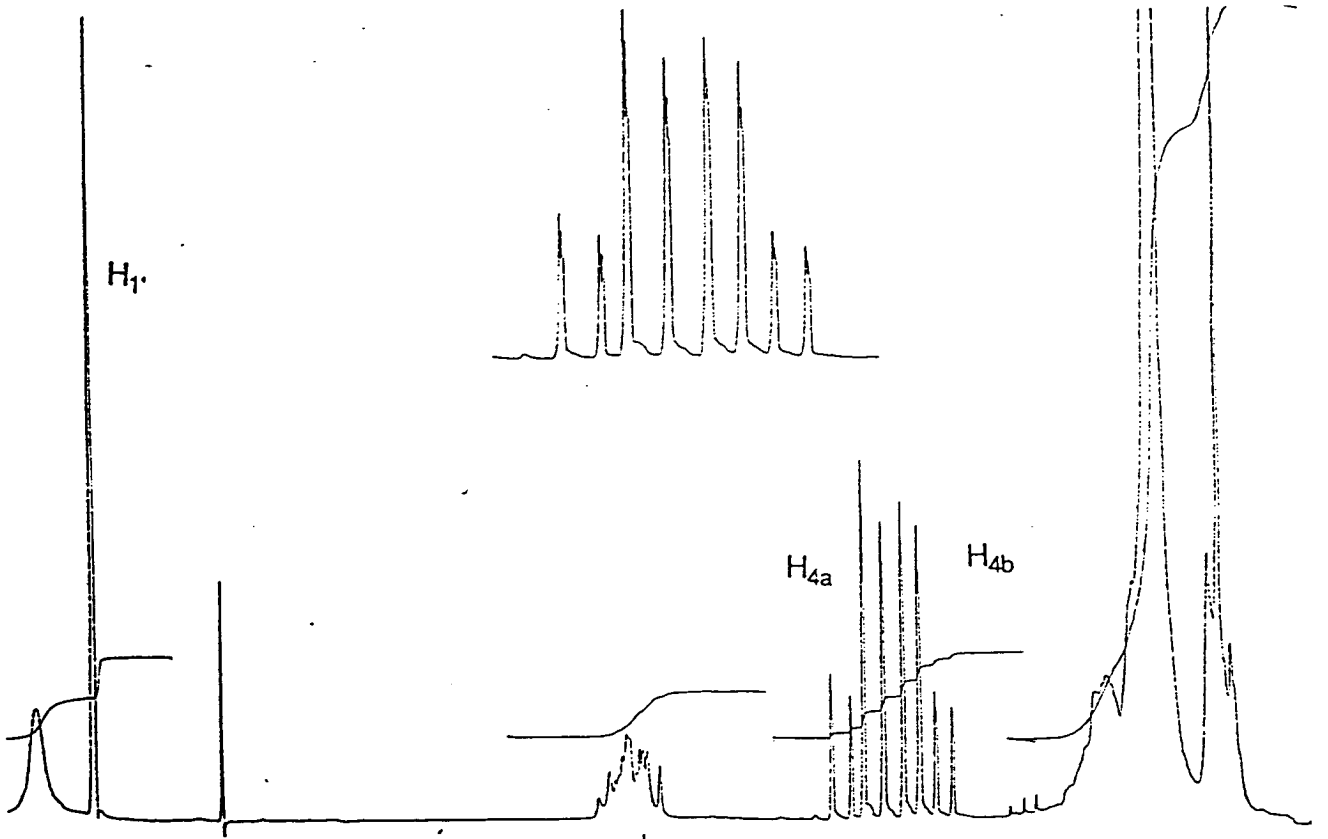
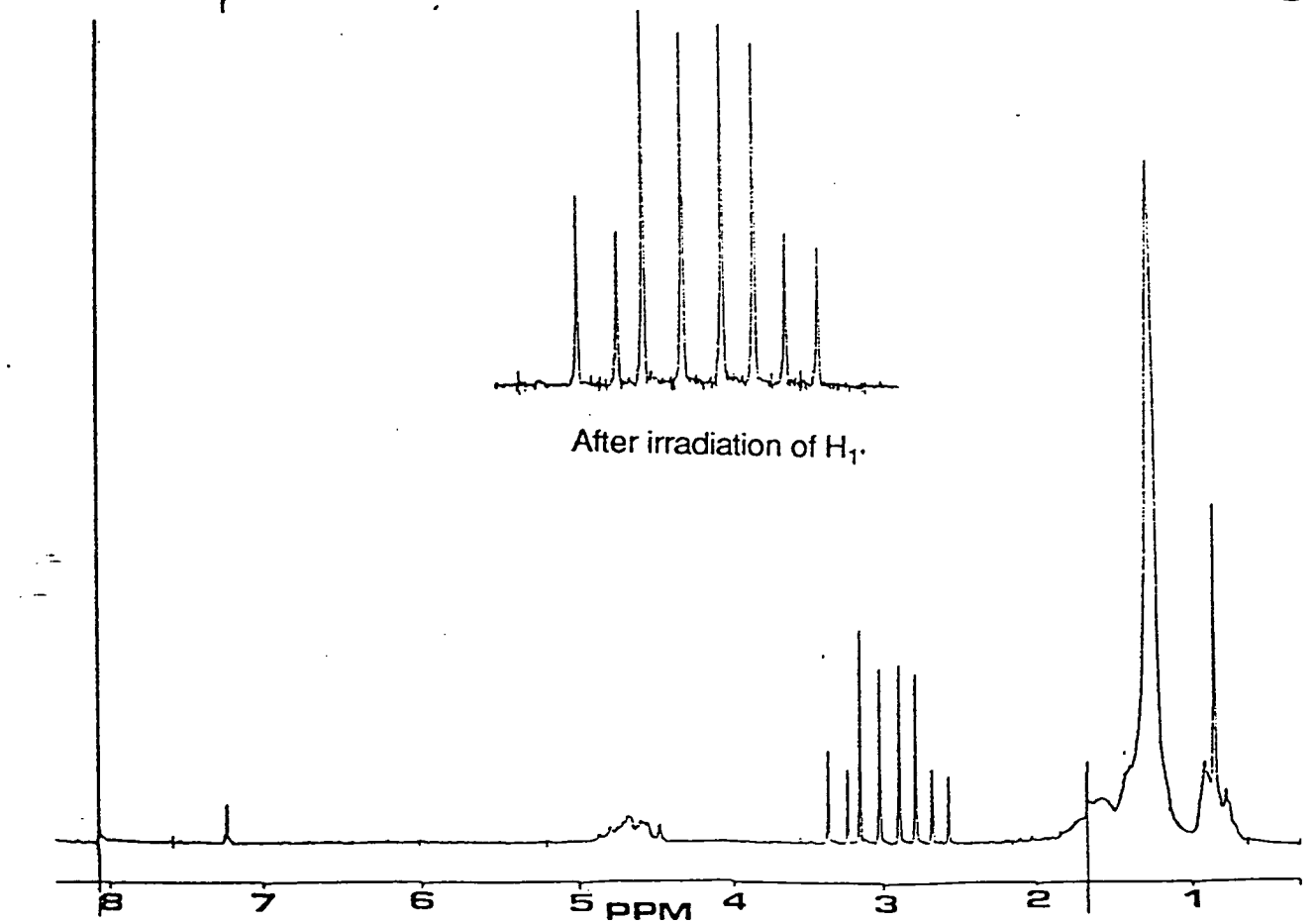

H4
H4
9
8
7
ppm
After irradiation of H1'

Fig. 40

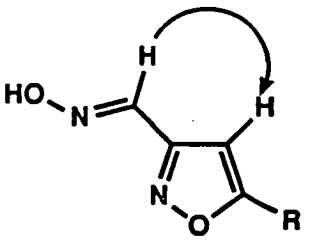


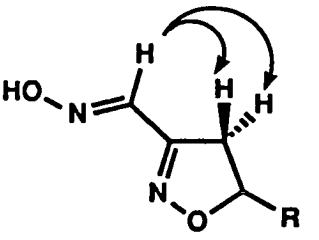




After irradiation of H_1·

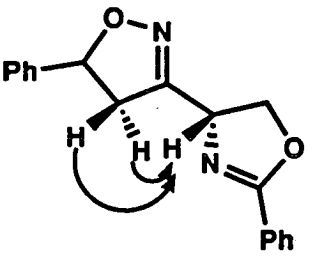
Fig. 41





	$J_{H4\,H1'}$ (Hz)		$J_{H4a/H4b\,H1'}$ (Hz)
R=Ph	0.4	R=Ph	0.7
R=C_8H_{17}	Not observed	R=C_8H_{17}	0.7

Fig. 39



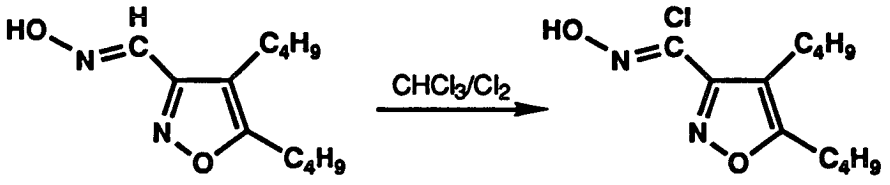
^4J=0.8 and 0.95Hz

Fig. 42

2.3.3. Generation and Cycloaddition Reactions of Isoxazole- and 2-Isoxazoline-3-carbonitrile oxides.

Initially the protocol which was envisaged for the conversion of the isoxazole and 2-isoxazoline oximes to the corresponding nitrile oxides was to chlorinate with chlorine gas, followed by isolation of the hydroximoyl chlorides and dehydrochlorination with triethylamine in the presence of the dipolarophiles. To this end aldoxime **(80a)** was treated with chlorine gas in chloroform at -5°C. However, despite consuming the oxime, no identifiable products could be isolated from the reaction

mixture. It is known that isoxazoles undergo electrophilic aromatic substitution reactions at the 4-position[138] and this may be a competing process in this reaction. In an attempt to test this hypothesis 3-aldoximino-4,5-dibutylisoxazole **(80e)**, which is not able to undergo this side reaction, was treated with a chloroform solution of chlorine according to the procedure employed by Dondoni *et al*[139] for the preparation of some thiazole hydroximoyl chlorides. The IR spectrum of the crude product showed an O-H stretching band (3250 cm^{-1}) and a strong signal at 760 cm^{-1}, which may have been due to C-Cl stretching. Treatment of a portion of the crude chlorination product with triethylamine resulted in the formation of a white precipitate which was assumed to be triethylamine hydrochloride. The oil obtained after the removal of the precipitate and solvent showed no O-H band in the IR spectrum; a strong signal appeared at 1620 cm^{-1} characteristic of furoxans.[140] This evidence is consistent with the formation of the isoxazole-3-hydroximoyl chloride **(81)** (scheme 66).

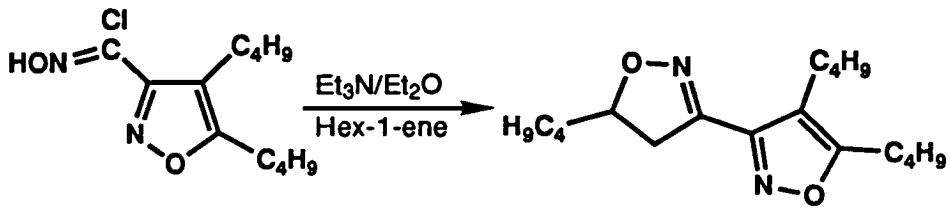


(80e) (81)

scheme 66

The remainder of the crude oil from the chlorination was dissolved in ether and treated with triethylamine in the presence of hex-1-ene. The ^{1}H-NMR spectrum (80 MHz) of the product from the reaction showed that some isoxazoline **(82)** had been formed (scheme 67) and thus

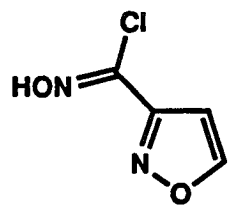
confirmed that the desired chloro-oxime had been produced. However, it was decided not to pursue this means of generating the nitrile oxides, since it requires the use of chlorine gas, and also results in messy reaction products which are difficult to purify. It is also not applicable when isoxazole rings with unsubstituted 4-positions are involved.



(81) (82)

scheme 67

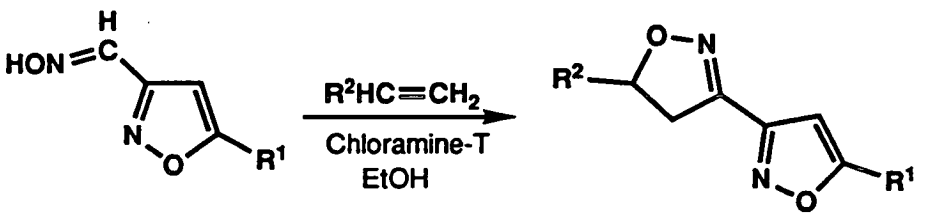
Various hydroximoyl chlorides are known to be toxic or severe irritants. Benzohydroximoyl chloride is a skin irritant and isoxazole hydroximoyl chloride **(70)** was reported to severely irritate the mucous membranes.[131]



(70)

Alternative methodology, which would allow the chloro-oxime to be generated *in situ*, were therefore investigated. The first *in situ* method to be tried was that reported by Hassner,[41] involving the use of chloramine-T (*N*-chloro-*N*-sodio-4-methylbenzenesulphonamide) to generate the nitrile oxide from the oxime. This process is thought to proceed by chlorination of the oxime followed by base catalysed

dehydrochlorination. The authors claim very high yields and only use one equivalent of chloramine-T for these reactions. When this protocol was investigated for the conversion of 3-aldoximino-5-phenylisoxazole **(80a)** and 3-aldoximino-5-octylisoxazole **(80b)** to the corresponding nitrile oxides, which were trapped with a suitable dipolarophile (scheme 68), yields were low and more than one equivalent of chloramine-T was required to achieve complete consumption of the oxime. A possible explanation for the need to add more than one equivalent of chloramine-T could be that it is reacting with the alkene to form the chlorohydrin,[141] although Hassner[41] discounts this possibility on the grounds that the hydroximoyl chloride is formed too rapidly to allow the chloramine-T to react with the olefin.



		Yield
(80a) R^1=Ph	(83) R^1=Ph, R^2=C_4H_9.	38%
(80b) R^1=C_8H_{17}	(84) R^1=R^2=C_8H_{17}	13%

scheme 68

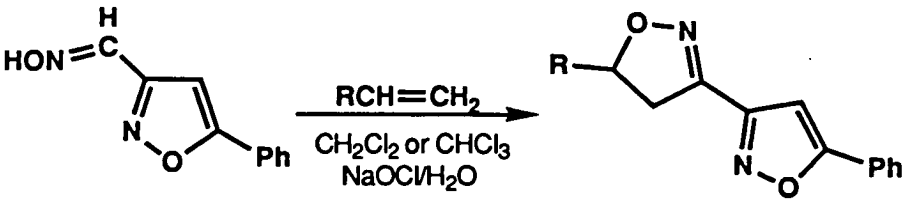
The very low yield obtained in the reaction of the nitrile oxide derived from **(80b)** and dec-1-ene is probably, in part, due to an inefficient recrystallisation. However, it was felt that the yields were too low for this method to be adopted for the generation of these heterocyclic nitrile oxides.

The second *in situ* method to be investigated was the use of aqueous sodium hypochlorite solution in a two phase system for the generation

and trapping of the 1,3-dipole.[35] This system was mainly applied to the generation of the isoxazole nitrile oxides and only one cycloaddition with 5-phenyl-2-isoxazoline-3-carbonitrile oxide was performed. The majority of these reactions were carried out with sodium hypochlorite solution, which was prepared by bubbling chlorine gas through an aqueous sodium hydroxide solution; however, in the three cycloaddition reactions with 2-vinylpyridine commercial sodium hypochlorite solution was used successfully.

The first reaction to be investigated was that of 3-aldoximino-5-phenylisoxazole (**80a**) with hex-1-ene, which furnished 5-butyl-3-(5-phenylisoxazol-3-yl)-2-isoxazoline (**83**) in 31% yield, after recrystallisation from hexane. This yield is comparable to that obtained with chloramine-T (38%). The same oxime was used in cycloaddition reactions with styrene, 2-vinylpyridine and dec-1-ene and the results are summarised in scheme 69. With the exception of adduct (**87**) the yields quoted are for recrystallised products. One of the features of this series of experiments is the difference in yields for the cycloaddition reactions with hex-1-ene and dec-1-ene, which should have similar reactivity. The difference in the yields is probably due to a better recovery of (**85**) from the recrystallisation. Compounds (**83**) and (**86**) were isolated by recrystallisation of the crude reaction product, while (**85**) and (**87**) were first flash column chromatographed.

The two yields quoted for the adduct of 2-vinylpyridine were recorded after chromatography; the first (44%) was the recovery when the sodium hypochlorite solution was added in one portion, the latter (53%) was obtained when the oxidant solution was added by syringe over twenty



(80a)

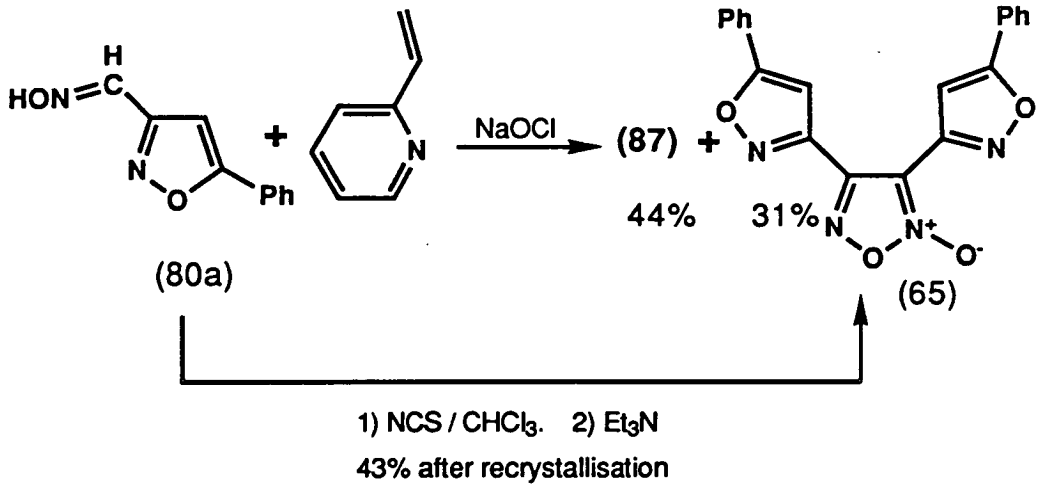
		Yield (%)
(83)	$R=C_4H_9$	31[1]
(85)	$R=C_8H_{17}$	51[1]
(86)	R=Ph	48[1]
(87)	R=2-Pyridyl	44[2] & 53[2]

1. Hypochlorite solution prepared in lab
2. Commercial hypochlorite solution used.

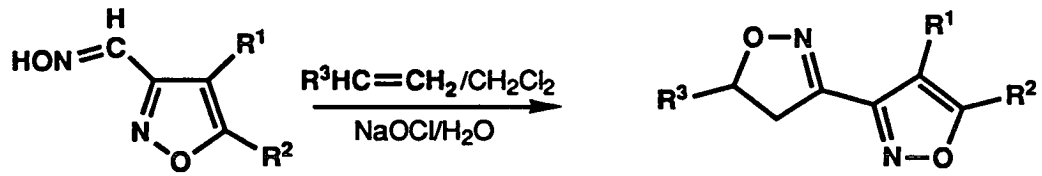
scheme 69

minutes. Thus by maintaining a lower concentration of the oxidising agent, yields can be slightly improved, presumably by minimising competing dimerisation reactions of the nitrile oxide. Indeed, in the 2-vinylpyridine cycloaddition reaction the furoxan **(65)** was isolated in 31% yield. This sample was identical to one prepared by generating the nitrile oxide in the absence of a dipolarophile (^{1}H-NMR, mp) (scheme 70).

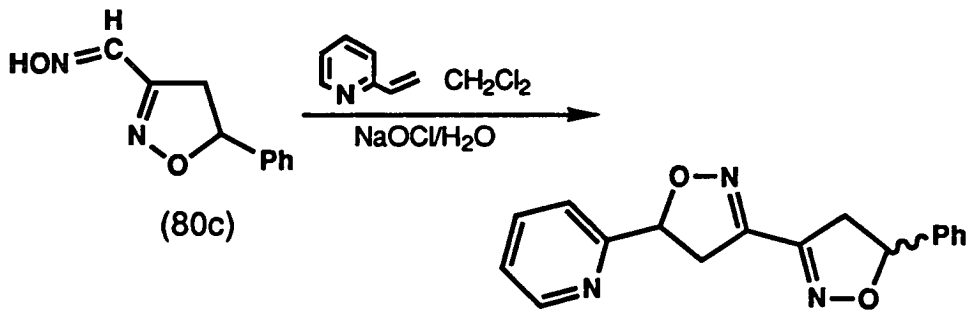
The hypochlorite protocol was also used to generate the nitrile oxide derived from 3-aldoximino-5-octylisoxazole **(80b)**, 3-aldoximino-4,5-dibutylisoxazole **(80e)** and 3-aldoximino-5-phenyl-2-isoxazoline **(80c)**. The results of these reactions are shown in scheme 71. Adducts **(89)** and **(82)** were both prepared on a small scale (*ca.* 100mg of oxime) using a sodium hypochlorite solution prepared in the laboratory. Both showed extremely clean conversion of oxime to the bis-heterocyclic adducts by tlc of the reaction mixture. The variation in isolated yields is attributed to more efficient isolation of adduct **(82)**.



scheme 70



		Yield (%)
(80b) R^1=H, R^2=C_8H_{17}	(88) R^1=H, R^2=C_8H_{17}, R^3= 	75
(80b) R^1=H, R^2=C_8H_{17}	(89) R^1=H, R^2=C_8H_{17}, R^3=C_4H_9	51
(80e) R^1= R^2 =C_4H_9	(82) R^1= R^2= R^3=C_4H_9	93



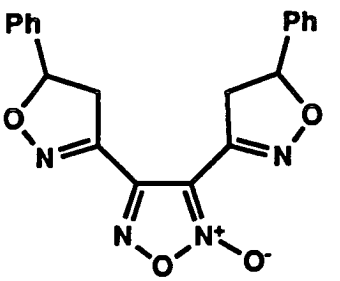
(80c)

(90)

scheme 71

The cycloaddition reaction between 5-octylisoxazole-3-carbonitrile oxide and 2-vinylpyridine utilised commercial sodium hypochlorite solution for the generation of the 1,3-dipole. The product was isolated as a clear oil in 75% yield after flash column chromatography. A portion of the product was converted to the hydrochloride salt by treatment with ethereal HCl to provide an analytical sample.

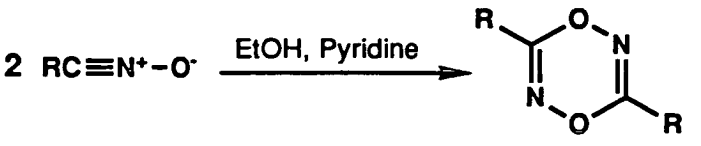
The final reaction in this series of experiments was the cycloaddition of 5-phenyl-2-isoxazoline-3-carbonitrile oxide, generated by treatment of aldoxime **(80c)** with commercial hypochlorite solution, with 2-vinylpyridine. This furnished cycloadduct **(90)** (scheme 71) in 50% yield presumably as a mixture of "*cis*" and "*trans*" isomers, although they could not be separated by tlc or flash chromatography. A second component isolated from this reaction, in 21% yield, was tentatively assigned as the furoxan **(91)**; this would also be expected to be a mixture of diastereomers. The structure was assigned on the basis of the mass spectrum which shows the required parent ion (E.I. M^+ 376, 6%) and the ^{1}H-NMR spectrum which shows isoxazoline peaks but no pyridyl signals.



(91)

In the presence of pyridine, nitrile oxides can also dimerise to 1,4,2,5-dioxadiazines[142] **(92)**. These reactions are reported to be high yielding when the solvent is ethanol, but yields drop markedly when apolar solvents are employed and the dimers would give the same parent ion in

the mass spectrum. The factors which mitigate against this structure (**92**)

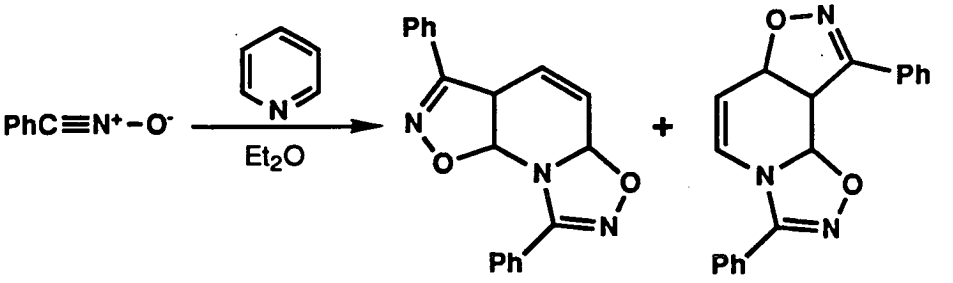


(92)

being the by-product in the present work are: firstly, the solvent was dichloromethane in which the yield of dioxadiazine would be expected to be low; secondly, in the cycloaddition reaction between 5-phenylisoxazole-3-carbonitrile oxide and 2-vinylpyridine the compound which was assigned the furoxan structure showed an identical ^{1}H-NMR spectrum to a sample prepared by generating the nitrile oxide in the absence of a dipolarophile where no pyridyl species were present; under these conditions the product would be expected to be the furoxan.

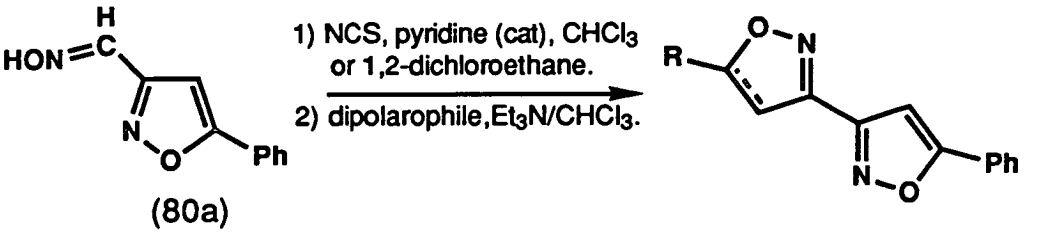
Pyridine is also reported to undergo cycloaddition reactions with nitrile oxides in apolar solvents[143] yielding adducts of the type shown in scheme 72. In the present work no such bis-adducts were observed, presumably because the terminal olefinic bond in 2-vinylpyridine provides a much more energetically favourable cycloaddition partner than the ring π-bonds, reaction of which would result in disruption of the aromatic system.

The final procedure to be investigated for the generation of isoxazole- and 2-isoxazoline-3-carbonitrile oxides involved treatment of a chloroform solution of the oxime with (NCS) together with a catalytic amount of pyridine to generate the hydroximoyl chloride, followed by dehydrochlorination in the presence of the dipolarophile with triethylamine.[40] All five oximes (**80a-e**) were reacted with a variety of



scheme 72

dipolarophiles using this protocol. The first oxime to be used was 3-aldoximino-5-phenylisoxazole **(80a)**. Four dipolarophiles were employed in this series: styrene, dec-1-ene, eicosene, and dec-1-yne and the results are summarised in scheme 73.



(80a)

Dipolarophile	Adduct	Yield (%)
$PhCH=CH_2$	(86) R=Ph	54[1]
$C_8H_{17}CH=CH_2$	(85) R=C_8H_{17}	51[1]
$C_{18}H_{37}CH=CH_2$	(93) R=$C_{18}H_{37}$	72[1]
$C_8H_{17}C\equiv CH$	(94) R=C_8H_{17}	40[2]

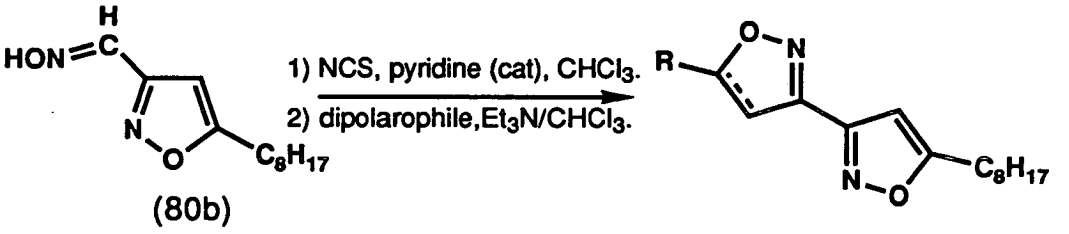
1.Yield from recrystallisation of crude reaction product.
2.Yield after chromatography.

scheme 73

In the literature procedure the conversion of the oxime to the hydroximoyl chloride with NCS[40] is carried out at 25°C; however, with oxime **(80a)** it

was found to work better at 40°C due to its lack of solubility in chloroform at room temperature. After the dipolarophile had been added, the solution of triethylamine was added over several hours by means of a syringe pump. Adducts **(85)**, **(86)** and **(93)** were isolated by recrystallisation of the crude reaction product, whereas bi-isoxazole **(94)** was obtained after flash column chromatography.

The same four dipolarophiles were next employed in the cycloaddition reaction with 5-octylisoxazole-3-carbonitrile oxide, generated by the NCS methodology from oxime **(80b)**. The outcome of this series of reactions is shown in scheme 74.



(80b)

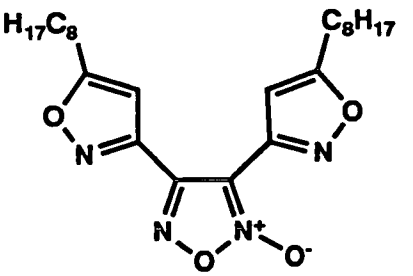
Dipolarophile	Adduct	Yield (%)
$PhCH{=}CH_2$	(95) R=Ph	72[1]
$C_8H_{17}CH{=}CH_2$	(84) R=C_8H_{17}	57[2]
$C_{18}H_{37}CH{=}CH_2$	(96) R=$C_{18}H_{37}$	62[1,3]
$C_8H_{17}C{\equiv}CH$	(97) R=C_8H_{17}	36[1]

1.Yield after chromatography. 2.Yield after recrystallisation.
3. 87% based on recovered oxime.

scheme 74

All of the adducts, apart from **(84)**, were isolated by flash column chromatography, and all were solids with relatively low melting points.

The reactions with the olefinic dipolarophiles furnished the isoxazole/isoxazoline adducts in moderate to good yields. With eicosene the product, 5-octadecyl-3-(5-octylisoxazole-3-yl)-2-isoxazoline **(96)**, was isolated in 62% yield. However, oxime **(80b)** was recovered from the reaction mixture suggesting that in this case the chlorination was incomplete; the yield based on consumed oxime was 87%. The low yield of bi-isoxazole **(97)** (36%) reflects the lower reactivity of acetylenic dipolarophiles. A small quantity of a by-product was recovered from this reaction. On the basis of its ^{1}H and ^{13}C-NMR spectra it is tentatively identified as the furoxan **(98)**.

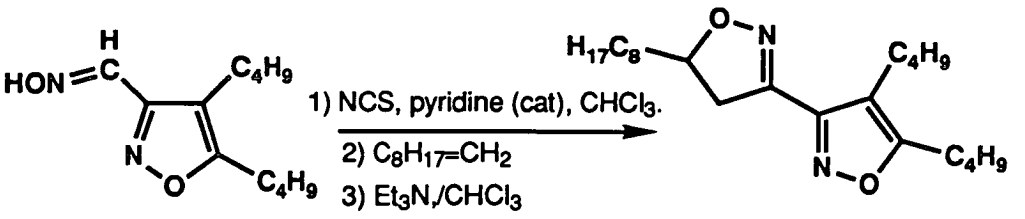


(98)

In the ^{1}H-NMR spectra of the adducts of 5-octylisoxazole-3-carbonitrile oxide the signal for H_4 of the isoxazole appears as a finely split triplet (J=0.8 Hz). Since this feature is not observed when the ring possesses a 5-phenyl substituent it seems likely that this is due to a ^{4}J long range coupling to the α-methylene of the octyl chain. Some selected ^{1}H and ^{13}C-NMR data for the adducts of the isoxazole-3-carbonitrile oxides are presented in tables 9,10 and 11.

The final isoxazole nitrile oxide to be generated by this procedure was 4,5-dibutylisoxazole-3-carbonitrile oxide from oxime **(80e)**. This was trapped with dec-1-ene, furnishing adduct **(99)** in 57% yield (78% based

on recovered oxime) (scheme 75). The isolation of some unreacted oxime again points to incomplete chlorination.



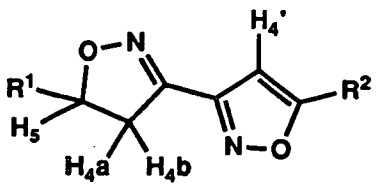
(80e) (99)

scheme 75

The NCS/Et_3N oxidation methodology was next applied to the generation of 5-phenyl- and 5-octyl-2-isoxazoline-3-carbonitrile oxides. The dipolarophiles employed in this series of reactions were dec-1-ene and styrene and the results are summarised in scheme 76.

Due to the presence of a chiral centre in the nitrile oxide and the generation of a second asymmetric carbon in the cycloadducts these compounds were isolated by flash chromatography as pairs of racemic diastereomers. Only in the case of 5-octyl-3-(5-phenyl-2-isoxazolin-3-yl)-2-isoxazoline **(100)**, which was prepared from both nitrile oxides, was complete separation, by flash chromatography, of the diastereomeric products possible. As expected the isolated ratios of the isomeric adducts was approximately 1:1; when 5-phenyl-2-isoxazoline-3-carbonitrile oxide was reacted with dec-1-ene the isolated ratio was 54:46, whereas for the reaction of 5-octyl-2-isoxazoline-3-carbonitrile oxide with styrene the same pair of isomeric products were formed in a ratio of 45:55 (scheme 77).

Table 9. Selected NMR data for the adducts of of isoxazole-3-carbonitrile oxides.



^{1}H-NMR

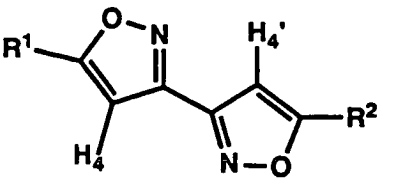
	$H_{4'}$	H_5	H_{4a}	H_{4b}
R^1=Ph	6.89(s)	5.79(dd)	3.88(dd)	3.42(dd)
R^2=Ph		*J*=10.9,8.9	*J*=17.4,10.9	*J*=17.4,8.9
R^1=C_8H_{17}	6.91(s)	4.8(m)	3.48(dd)	3.02(dd)
R^2=Ph			*J*=17.2,10.3	*J*=17.2,8.7
R^1=Ph	6.44(t)	5.75(dd)	3.82(dd)	3.36(dd)
R^2=C_8H_{17}	*J*=0.8	*J*=10.9,8.8	*J*=17.4,10.9	*J*=17.4,8.8
R^1=C_8H_{17}	6.36(t)	4.68(m)	3.41(dd)	2.96(dd)
R^2=C_8H_{17}	*J*=0.8		*J*=17.2,10.3	*J*=17.2,8.6

^{13}C-NMR

	$C_{3'}$	$C_{4'}$	$C_{5'}$	C_3	C_4	C_5
R^1=Ph	170.3[1]	97.2	155.5[1]	149.2	41.5	83.4
R^2=Ph						
R^1=C_8H_{17}	170.2	97.2	156.0	149.4	38.7	82.6
R^2=Ph						
R^1=Ph	174.4	98.7	155.0	149.4	41.7	83.2
R^2=C_8H_{17}						
R^1=C_8H_{17}	174.3	98.6	155.5	149.6	38.7	82.4
R^2=C_8H_{17}						

1. The assignment of $C_{3'}$ and $C_{5'}$ is tentative and is based on the assignment of Buchan *et al.*[144]

Table 10. Selected NMR data for 5,5'-substituted biisoxazoles.



^{1}H-NMR

	$H_{4'}$	H_4
$R^1=C_8H_{17}$ R^2=Ph	6.99 (s)	6.55[1] (s)
$R^1=C_8H_{17}$ $R^2=C_8H_{17}$	6.44 (t) J= 0.75	

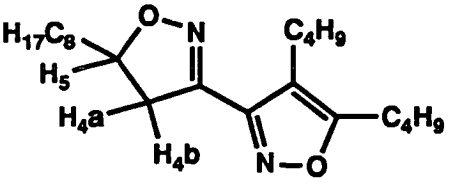
1. ^4J coupling is not observed but the H_4 signal is slightly broadened

^{13}C-NMR

	$C_{3'}$	$C_{4'}$	$C_{5'}$	C_3	C_4	C_5
$R^1=C_8H_{17}$ R^2=Ph	170.6	97.4	154.9[1]	174.8	98.9	154.0[1]
$R^1=C_8H_{17}$ $R^2=C_8H_{17}$	174.6	98.9	154.3	174.6	98.9	154.3

1.uncertain assignment

Table 11. Selected NMR data for adduct (99)

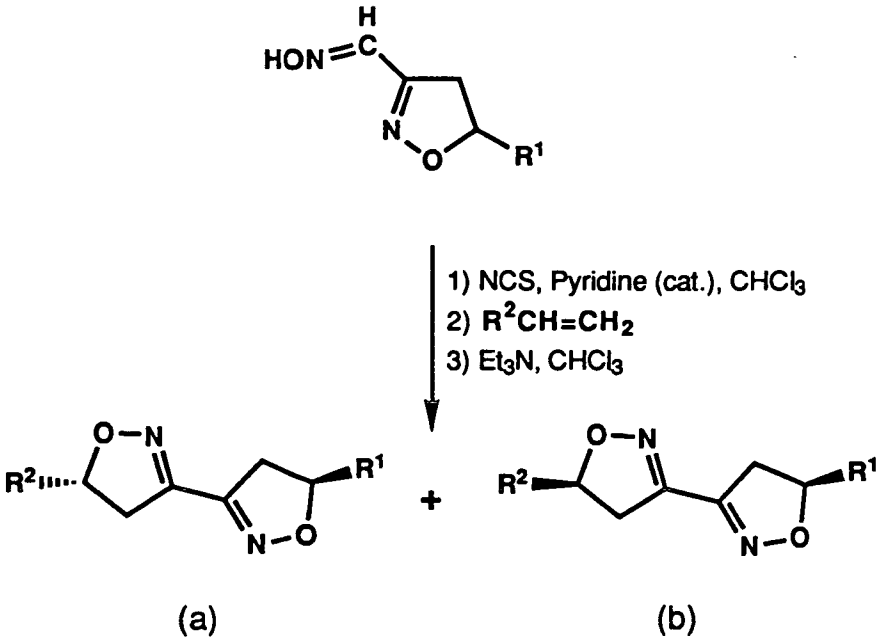


^{1}H-NMR

H_5	H_{4a}	H_{4b}
4.46 (m)	3.41 (dd) J=17.1, 10.5	3.03 (dd) J=17.1, 8.4

^{13}C-NMR

$C_{3'}$	$C_{4'}$	$C_{5'}$	C_3	C_4	C_5
169.9	113.8	154.4	150.3	39.9	81.2



(only one enantiomer is shown for each of the products)

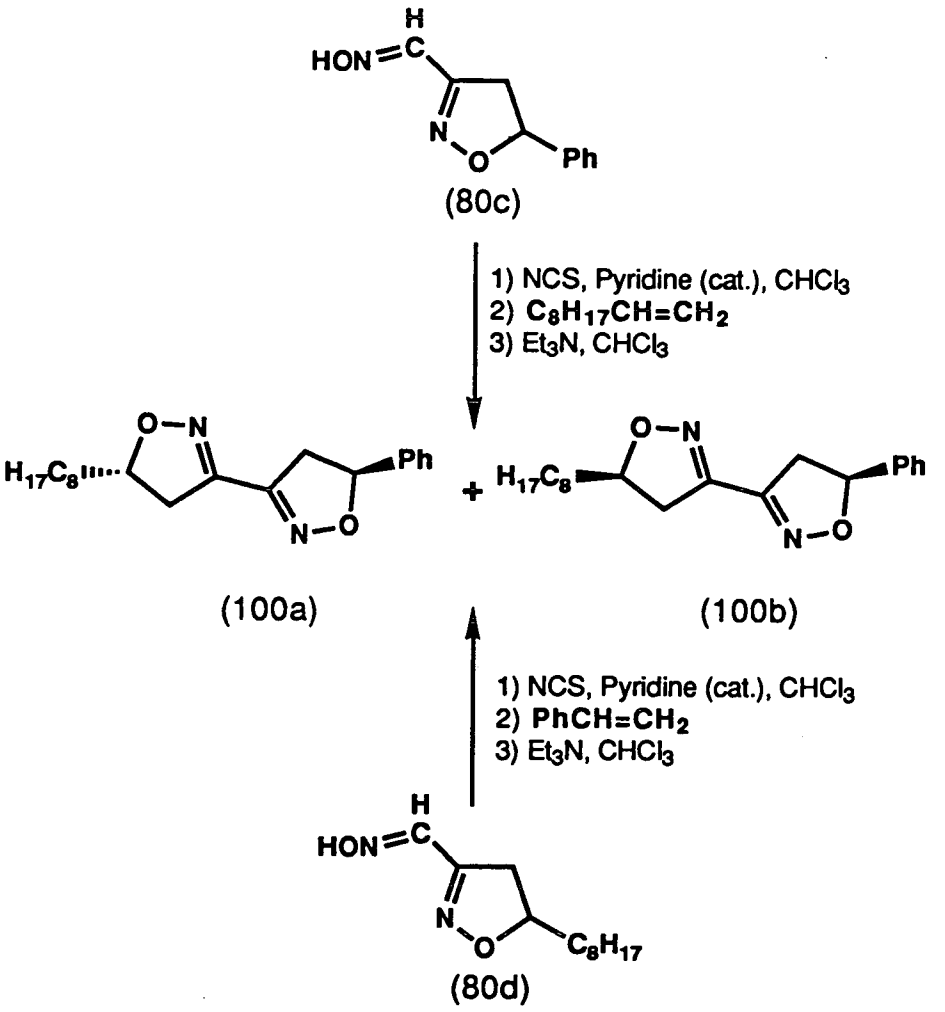
			Yield (%)
(66)	R^1=Ph,	R^2=Ph	46[1]
(100)	R^1=Ph,	R^2=C_8H_{17}	53
(100)	R^1=C_8H_{17},	R^2=Ph	35
(101)	R^1=C_8H_{17},	R^2=C_8H_{17}	58

1. 59% based on recovered starting material

scheme 76

Both of the diastereomeric adducts **(100a & 100b)** were isolated as white solids (m.p.78-79.5 and 69-70°C, respectively), which showed a tendency to form gels with the recrystallisation solvents. Their ^{1}H and ^{13}C-NMR spectra are virtually identical, making accurate determination of the isomer ratio by NMR difficult.

It is worthy of note that in the cycloaddition reaction of 5-octyl-2-isoxazoline-3-carbonitrile oxide with styrene a small amount of impure 3-formyl-5-octyl-2-isoxazoline **(79d)**, probably contaminated with some



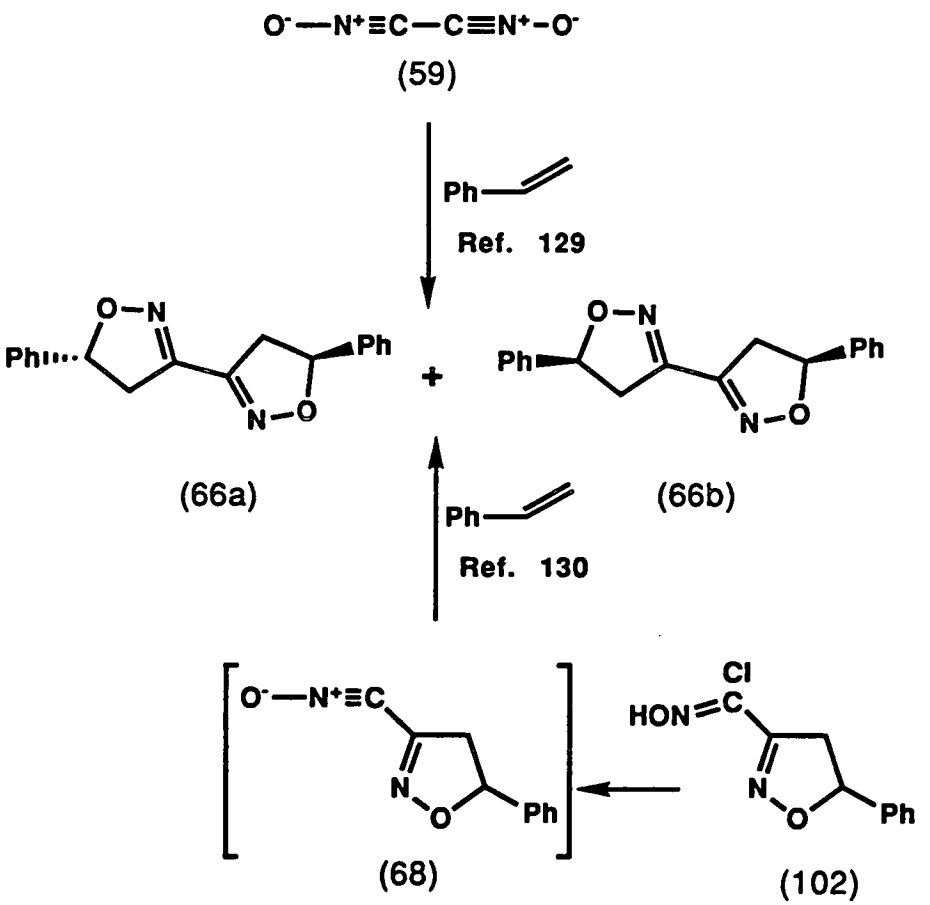
(only one enantiomer is shown for each of the products)

scheme 77

styrene, was also isolated (*ca.* 28%). This may have been due to some hydrolysis of the oxime or the hydroximoyl chloride brought about by a trace of water in the reaction mixture. This, in part, explains the low yield from the reaction.

The two symmetrical cycloadducts 5-phenyl-3-(5-phenyl-2-isoxazolin-3-yl)-2-isoxazoline **(66)** and 5-octyl-3-(5-octyl-2-isoxazolin-3-yl)-2-isoxazoline **(101)** were prepared in moderate yields, 46% (59% based on recovered oxime) and 58%, respectively. The bis-heterocycle **(66)**

has previously been reported in the literature.[129 130] The approach of Grundmann[129] involved the reaction of styrene with oxalodinitrile oxide **(59)** (sect. 2.3.1.1). In contrast, the method employed by Finzi[130] made use of the hydroximoyl chloride **(102)** derived from oxime **(80c)** (sect. 2.3.1.2) as a source of the nitrile oxide **(68)** (scheme 78). In both reports a pair of diastereomeric bi-isoxazolines were isolated, however, neither of these groups established the stereochemistry of the isomeric products.



(only one enantiomer is shown for each of the products)

scheme 78

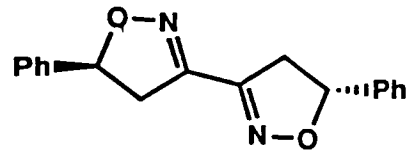
After partial separation of the diastereomers **(66a)** and **(66b)** by flash column chromatography a suitable crystal for *X*-ray structure (Fig. 43) was obtained for the first eluted and higher melting isomer (m.p. 169-

172°C, lit.,[129] 174-175°C). This proved to be the *RS/SR-meso*-adduct **(66a)**, thus the slower eluting lower melting isomer **(66b)** (m.p. 98-99°C, lit.,[129] 96-97°C) has the *RR/SS*-configuration.

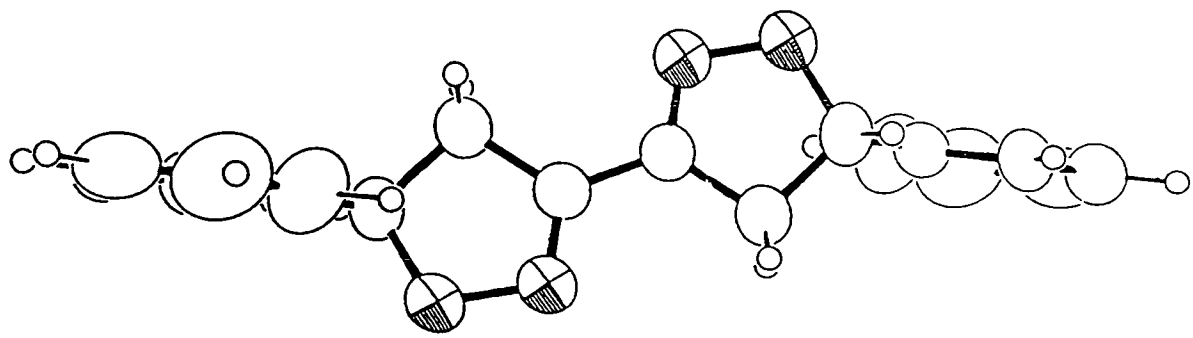
By analogy with this result the stereochemistry of the racemic diastereomeric pair of adducts formed in the cycloaddition reaction of 5-octyl-2-isoxazoline-3-carbonitrile oxide with dec-1-ene can be tentatively assigned; the first eluted higher melting isomer (m.p. 124-125°C) is assigned as the *RS/SR-meso*-adduct **(101a)**, while the slower eluting isomer (m.p. 113-114°C) is the *SS/RR*-bis-heterocycle **(101b)**. The ratio of non-symmetrical bi-isoxazoline adducts **(100a & b)**, which were separated completely by column chromatography, was approximately 1:1. This is consistent with previous literature reports[74-76] for the addition of chiral nitrile oxides with achiral olefins; in all cases there is poor π-facial stereoinduction. Furthermore in those examples reported, the asymmetric carbon is located immediately adjacent to the nitrile oxide moiety, while in the present examples it is three carbons removed. Its influence on selectivity is therefore expected to be even less.

2.3.4. Observations from the *X*-Ray Structure of *RS/SR-meso*-5-phenyl-3-(5-phenyl-2-isoxazolin-3-yl)-2-isoxazoline (66a).

The *X*-ray crystal structure of **(66a)** shows that the two isoxazoline rings are almost coplanar. The ring nitrogens adopt a "transoid" arrangement with respect to each other; presumably this allows the molecule to profit from conjugative overlap between the C=N π-systems while avoiding steric interactions between the H_4 and $H_{4'}$ protons which would occur if a "cisoid" conformation was adopted. The phenyl rings are rotated to an angle of approximately 55° with respect to the heterocyclic rings.



66a



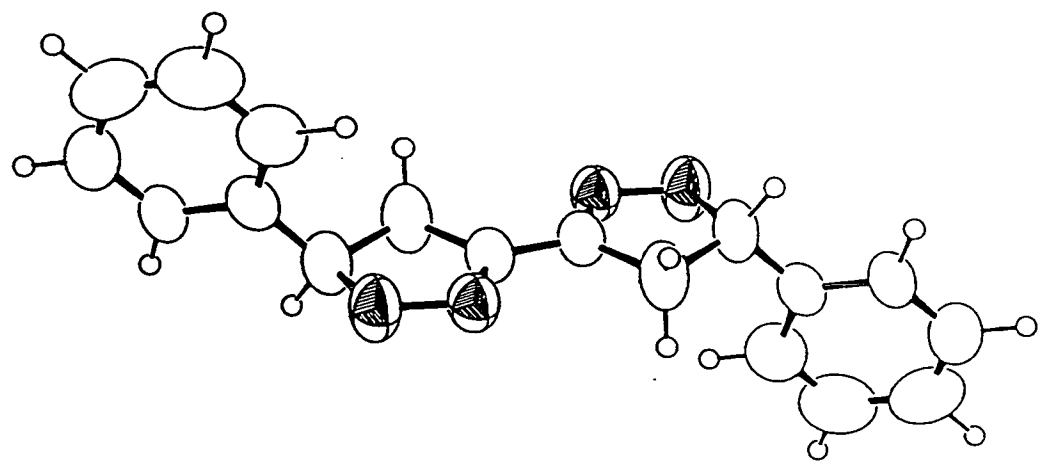


Fig 43

2.3.5. Conclusions.

A range of isoxazole- and 2-isoxazoline-3-aldoximes were successfully prepared in good yield from readily available olefins and ethoxycarbonylformonitrile oxide. Four methods were investigated for the conversion of these aldoximes to nitrile oxides, which were subsequently trapped with a range of alkenes and alkynes.

The first procedure to be investigated, involving treatment of the oxime with chlorine gas followed by isolation and further reaction with triethylamine and a dipolarophile, was singularly unsuccessful and suffers from the added disadvantage of requiring the use of chlorine gas. The use of chloramine-T for *in situ* generation of the nitrile oxides did furnish the desired products in the few cases examined; however, yields were found to be poor.

The final two procedures proved to be most successful. Generation of the nitrile oxides in a two phase system with aqueous sodium hypochlorite furnished the bis-heterocyclic adducts in reasonable yields. One of the attractive features of this protocol is that commercial bleach can be used and the work up is very straight-forward; it requires only separation of the aqueous phase, drying and removal of the solvent (CH_2Cl_2) which affords a solid from which the product can often be obtained by recrystallisation.

The use of NCS for the formation of the hydroximoyl chloride followed by dehydrochlorination with triethylamine in the presence of the dipolarophile also furnished most of the cycloadducts in reasonable to good yields. This procedure has the advantage of higher yields compared with the hypochlorite methodology; however, this is offset by the more straight-forward experimental procedure for the two phase system and the shorter reaction times required. Thus there is little to choose between the latter two procedures, but the ability to use commercial bleach in the two phase system does perhaps give it a slight

advantage.

At the time of writing none of these compounds had been tested as potential oil additives.

3. Experimental.

3.1. General Experimental Conditions.

3.1.1. Instrumentation.

Elemental analyses were performed by Mrs E. McDougall using a Carlo Erba elemental analyser model 1106, Butterworths Laboratories, Teddington Middlesex, or Medac Ltd, Brunel University, Uxbridge, Middlesex.

Infra-red spectra were recorded as films or Nujol mulls on a Perkin Elmer 781 spectrometer.

Nominal mass E.I. mass spectra were recorded on a Kratos MS902 instrument by Miss E. Stevenson. FAB mass spectra (nominal and accurate mass) and accurate mass E.I. spectra were recorded by Mr A. Taylor on a Kratos MS50TC instrument.

Melting points were measured on a Gallenkamp capillary tube apparatus and are uncorrected.

^{1}H-NMR spectra were recorded on Bruker WP80Y, WP200Y, AC300E and WH360 instruments by Mrs H.Grant, Mr J.R.A Millar and Dr D. Reed. Chiral shift experiments were carried out on the WH360.

^{13}C-NMR were recorded on the WP200Y, AC300E and WH360 instruments.

Chemical shifts (δ) in all spectra are measured in parts per million using tetramethylsilane (δ=0.0) as the referance signal.

Optical rotations were measured on a Perkin Elmer 141 polarimeter using 2 ml of filtered solution.

X-ray diffraction analyses were carried out on a Stoe STADI-4 four circle diffractometer by Dr A. Blake and Dr R. O. Gould.

3.1.2. Chromatography.

High pressure liquid chromatography was carried out on a Cecil Instruments CE 212 variable wavelength U.V. monitor at 254 nm and an Altex model 110A pump.

Preparative thin layer chromatography was carried out on glass plates (20 x 20 cm) coated with a layer of Kieselgel GF_{254} (0.5 mm) which contains 13% calcium sulphate and a fluorescent indicator.

Analytical thin layer chromatography was carried out on Merck aluminium backed plates coated with Kieselgel GF_{254} (0.2 mm).

Dry flash chromatography was carried out with a variety of sintered funnels filled with Kieselgel GF_{254} and eluted under water pump vacuum.

Flash column chromatography was carried out with Kieselgel 60 (230-400 mesh) and eluted under nitrogen at 2-5 psi.

3.1.3. Solvents and Reagents.

All reagents and solvents were standard laboratory grade and were used as supplied unless otherwise stated.

Dry benzene was Analar grade dried over sodium wire.

Dry acetone was Analar grade solvent stored over 4A molecular sieve.

Pyridine was dried by distillation from and stored over potassium hydroxide.

Dry dichloromethane was freshly distilled from calcium hydride.

Dry THF and ether were freshly distilled from sodium and benzophenone.

Dry methanol was HPLC grade solvent.

Dry ethanol was obtained by distillation from magnesium ethoxide.

Dry chloroform was obtained by distillation from phosphorus pentoxide.

Dry DMSO was obtained by distillation under water pump vacuum from calcium hydride.

Solvents for HPLC analysis were of the appropriate grade and were

degased before use.

3.2. Compounds for General Use.

3.2.1. Ethyl chloro-oximidoacetate

The title compound was prepared according to the procedure of Skinner[135] with some minor modifications.

To a well stirred solution of glycine ethyl ester hydrochloride (30 g, 0.21 mmol) in water (90 ml) cooled with an ice/salt bath to *ca.* -5°C was added concentrated hydrochloric acid (36% w/w, 21.3 g, 0.21 mmol) followed by dropwise addition of a solution of sodium nitrite (14.5 g, 0.21 mmol) in water (25 ml). The additions of hydrochloric acid and sodium nitrite were repeated with the same quantities. After stirring for one hour the insoluble yellow oil which had formed was extracted into ether (2 x 80 ml); the combined extract was dried over $MgSO_4$ and the solvent removed *in vacuo,* furnishing a yellow oil which was dissolved in hexane with the minimum of ether added and stored in the freezer overnight. The resulting off-white solid was filtered and recrystallised from ether/hexane to afford a white crystalline solid (14.3 g, 44%) m.p. 79-82°C (lit.,[135] 80°C).

3.2.2. Benzohydroximoyl chloride.

The title compound was prepared by the method of Chiang[145] with some modifications.

Chlorine gas was bubbled through a solution of benzaldoxime (20.6 g, 0.17 mmol) in chloroform (500 ml) which was maintained at *ca.* -5°C (ice/salt bath) until the solution assumed a yellow colour (having gone first from blue to green). Nitrogen gas was bubbled through the solution for one hour to displace excess chlorine before removing the solvent under reduced pressure. The residual oil was solidified in the freezer

overnight, then recrystallised from pentane to afford a white crystalline solid (22.4 g, 85%) m.p. 47-51°C (lit.,[145] 50-51°C).

3.2.3. Dibromoformaldoxime.

The title oxime was prepared by a literature procedure.[99]

To a stirred solution of glyoxylic acid hydrate (10 g, 135 mmol) in water at room temperature was added hydroxylamine hydrochloride (9.25 g, 137 mmol). After stirring for 24 hours sodium hydrogen carbonate (23.5 g, 280 mmol) was carefully added followed by dichloromethane (100 ml); the resulting two phase system was cooled to approximately 6°C and, with vigorous stirring, bromine (29.9 g, 9.64 ml, 187 mmol) in dichloromethane (50 ml) added at such a rate that the temperature did not exceed 10°C. Stirring was continued for three hours before separating the organic phase and extracting the aqueous portion with dichloromethane (3 x 50 ml). The combined organic extract was dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was recrystallised from *n*-hexane to yield a white crystalline solid (4.8 g, 18%) m.p. 67-69°C (lit.,[99] 65-66°C).

3.3. Synthesis and Cycloaddition Reactions of (4*R*)-3-(*N*-*t*-butoxycarbonyl)-2,2-dimethyl-4-vinyloxazolidine (12) and (2*R*)-2-(*N*-*t*-butoxycarbonylamino)but-3-en-1-ol (13).

3.3.1. *N*-Boc-(*S*)-serine methyl ester (16).

To a stirred solution of (*S*)-serine methyl ester hydrochloride (10.0 g, 64 mmol) in dry pyridine (150 ml) was added in portions over 15 minutes di-*t*-butyl dicarbonate (22.9 g, 105 mmol) at room temperature. After 12 hours the reaction mixture was concentrated *in vacuo*, poured into water and extracted with ethyl acetate (3 x 100 ml). The combined extract was washed with 10% aqueous potassium hydrogen sulphate (2 x 100 ml),

dried over $MgSO_4$ and the solvent removed by rotary evaporation affording the title compound as a viscous oil (13.8 g, 98%) $\nu_{max.}$ 3540 (O-H), 1740, 1710 cm^{-1} (C=O); δ_H (80 MHz; $CDCl_3$) 5.52-5.42 (1H, br.d, NH), 4.40-4.21 (1H, br.m, H_2), 3.78 (2H, br.d, H_3), 3.0-2.25 (1H, br.s, OH), 1.40 (9H, s, *t*-Bu); δ_C (50 MHz; $CDCl_3$) 171.3 (C=O, $_{ester}$), 155.6 (C=O, $_{Boc}$), 80.2 ($OCMe_3$), 63.2, 55.6 (C_2, C_3), 52.4 (CH_3O), 28.1 ($OCMe_3$); m/z (FAB ms) 220 [(*M*+H)$^+$].

3.3.2. (4*S*)-3-(*N*-*t*-butoxycarbonyl)-2,2-dimethyl-4-methoxycarbonyl-oxazolidine (17).

The title compound was prepared according to the procedure of Garner and Park.[101]

A solution of *N*-Boc-(*S*)-serine methyl ester (**16**) (13.8 g, 63 mmol), 2,2-dimethoxypropane (13.52 g, 130 mmol) and *p*-toluenesulphonic acid (0.17 g, 0.88 mmol) in benzene (220 ml) was refluxed for 30 minutes and then slowly distilled until a volume of 190 ml had been collected. To the residue in the reaction flask was added 2,2-dimethoxypropane (5.5 g, 53 mmol) and benzene (90 ml) and the process repeated, this time collecting 77 ml of distillate. The cooled residue was partitioned between saturated sodium hydrogen carbonate solution (60 ml) and ether (200 ml); the organic portion was washed with saturated sodium hydrogen carbonate (160 ml), brine (100 ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. The residual amber oil was distilled b.p. 69-74°C/0.1 mmHg (lit.,[101] 101-102°C/2 mmHg) affording a clear oil (12.7 g, 78%); $[\alpha]_D$ (20°C) -56.3° (c 2.0 in $CHCl_3$) (lit.,[101] $[\alpha]_D$ -46.7° (c 1.3 in $CHCl_3$)); $\nu_{max.}$ (neat) 1760, 1710 cm^{-1} (C=O); δ_H (200 MHz; $CDCl_3$, 25°C) (all of the peaks are doubled due to flipping of the oxazolidine ring, this is consistent with

previous observations[101]) 4.39 and 4.28 (1H, 2dd, *J* 2.8, 3.2, 6.5, 6.9 Hz, H_4), 4.09-3.88 (2H, m, H_{5a} and H_{5b}), 3.65_2 and 3.64_9 (3H, 2s, MeO), 1.56, 1.53, 1.42, 1.39, 1.31 (15H, 5s, $OC(CH_3)_2N$, *t*-Bu); δ_H (200 MHz; C_6D_6, 75°C) 4.28 (1H, br.s, H_4), 3.81 (2H, br.s, H_{5a} and H_{5b}), 3.41 (3H, br.s, MeO), 1.71 (3H, br.s, CH_3), 1.48 (3H, br.s, CH_3), 1.38 (9H, br.s, *t*-Bu); δ_C (50 MHz; $CDCl_3$, 25°C) 171.3, 170.9 (C=O, $_{ester}$), 151.7, 150.9 (C=O, $_{Boc}$), 94.7, 94.0 (C_2), 80.5, 79.9 ($OCMe_3$), 65.9, 65.7 (C_5), 58.9 (C_4), 52.0 (MeO), 27.9 ($OCMe_3$), 25.7, 24.8, 24.6, 24.0 ($OC(CH_3)_2N$); δ_C (50 MHz; C_6D_6, 80°C) 171.3 (C=O, $_{ester}$), 151.6 (C=O, $_{Boc}$), 95.2 (C_2), 80.0 ($OCMe_3$), 66.4 (C_5), 59.9 (C_4), 51.5 (MeO), 28.4 ($OCMe_3$), 25.6, 25.1 ($OC(CH_3)_2N$); m/z (FAB ms) 260 [$(M+H)^+$].

3.3.3. (4*S*)-3-(*N*-*t*-butoxycarbonyl)-2,2-dimethyl-4-formyloxazolidine (**18**)

The title aldehyde was prepared by the procedure of Garner and Park.[101] To a stirred solution of the oxazolidine ester (**17**) (12.73 g, 49 mmol) in dry toluene (110 ml), at -78°C under a nitrogen atmosphere, was added dropwise, a solution of DIBAL (1M in hexanes, 122.5 ml, 122 mmol) at such a rate that the temperature did not exceed -68°C. Stirring was continued for 3 hours before quenching with methanol (9 ml), keeping the internal temperature below -65°C. The reaction was allowed to warm to room temperature, poured into ice-cold 1 molar HCl (500 ml), and extracted with ethyl acetate (3 x 300 ml); the combined organic extract was washed with brine (2 x 250 ml), dried over $MgSO_4$ and the solvent removed *in vacuo* affording 11.5 g of a yellowish oil. Kugelrohr distillation, (120°C/0.1 mmHg) gave a colourless oil (9.9 g, 88%), (Found: $(M+H)^+$ 230.13922. Calc. for $C_{11}H_{20}NO_4$ (*M*+H), 230.13922); $[\alpha]_D$ (20°C) -75.8° (c 1.05 in $CHCl_3$) (lit.,[101] $[\alpha]_D$ -91.7° (c 1.34 in $CHCl_3$)). ^{1}H-NMR showed that

the aldehyde was not pure, however, it was used in subsequent reactions without further purification.

3.3.4. (4*R*)-3-(*N*-*t*-butoxycarbonyl)-2,2-dimethyl-4-vinyloxazolidine (**12**).

To a suspension of methyltriphenylphosphonium iodide (10.58 g, 26.2 mmol) in dry THF (50 ml) under a nitrogen atmosphere, was added a solution of potassium-*t*-butoxide (2.94 g, 26.2 mmol) in dry THF (25 ml). The yellow suspension which formed was stirred at room temperature for 2 hours before adding a solution of aldehyde (**18**) (3.0 g, 13.1 mmol) in dry THF (40 ml) over 5 minutes. The reaction mixture was stirred overnight, then heated to reflux for 30 minutes, cooled to room temperature and quenched with water (50 ml). Most of the THF was removed by rotary evaporation and the residue extracted with ethyl acetate (3 x 50 ml); the combined organic extract was washed with brine (100 ml), dried over $MgSO_4$ and the solvent removed *in vacuo* yielding an oil which was subjected to flash column chromatography (EtOAc/hexane, 4:96) affording alkene (**12**) as a clear oil (1.96 g, 66%). A sample was Kugelrohr distilled (80°C/0.1 mmHg) for optical rotation $[\alpha]_D$ (20°C) +14.98° (c 2.5 in $CHCl_3$), (lit.,[102] $[\alpha]_D$ (28°C) +15° (c 2.5 in $CHCl_3$); $\nu_{max.}$ (neat) 1700 cm^{-1} (C=O); δ_H (200 MHz; C_6D_6, 80°C) 5.74 (1H, ddd, *J* 17.2, 10.1, 6.9 Hz, H_2C=C*H*-), 5.12-5.05 (1H, m, *H*$_2$C=CH-), 5.0-4.94 (1H, m, *H*$_2$C=CH-), 4.25-4.10 (1H, m, H_4), 3.72 (1H, dd, J_{H5aH5b} 8.7 Hz, J_{H5aH4} 6.3 Hz, H_{5a}), 3.50 (1H, dd, J_{H5bH5a} 8.7 Hz, J_{H5bH4} 2.5 Hz, H_{5b}), 1.70 (3H, s, CH_3), 1.57 (3H, s, CH_3), 1.45 (9H, s, *t*-Bu); δ_C (50 MHz; C_6D_6, 79°C)[1] 138.5 (H_2C=*C*H), 115.2 (*H*$_2$*C*=CH-), 94.3 (C_2), 79.4 (Me_3CO), 68.4 (C_5), 60.0 (C_4), 28.6 (*Me*$_3$*C*O), 27.1 (CH_3), 24.6 (CH_3); m/z (FAB ms) 228 [(*M*+H)$^+$].

1. The carbonyl carbon of the Boc group is not seen in the ^{13}C spectrum at elevated temperature. At room temperature it occurs at 151.9 ppm.

3.3.5. (2*R*)-2-(*N*-*t*-butoxycarbonylamino)but-3-en-1-ol (**13**).

A solution of (4*R*)-3-(*N*-*t*-butoxycarbonyl)-2,2-dimethyl-4-vinyloxazolidine (**12**) (300 mg, 1.32 mmol) and *p*-toluenesulphonic acid (38 mg, 0.2 mmol) in methanol (10 ml) was stirred at room temperature for 36 hours, at which time tlc (EtOAc/hexane, 1:1, viewing neutral $KMnO_4$) indicated complete consumption of the starting material. The solution was concentrated under reduced pressure, dissolved in ethyl acetate and washed with 10% aqueous sodium carbonate solution (2 x 20 ml), water (2 x 20 ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Flash column chromatography of the residue (EtOAc/hexane, 7:3 then 1:1) furnished a clear oil which solidified on standing (187 mg, 76%) m.p. 32-37°C (lit.,[146] 36-37°C); $[\alpha]_D$ (20°C) +26.3° (c 1.48 in $CHCl_3$), (lit.,[102] $[\alpha]_D$ (26°C) +29° (c 2.1 in $CHCl_3$)); $\nu_{max.}$ (neat) 3400 (O-H/N-H), 1690 (C=O), 1650 cm^{-1} (C=C); δ_H (200 MHz; $CDCl_3$, 65°C) 5.81 (1H, ddd, J_{H3H2} 5.4 Hz, $J_{H3H4b(cis)}$ 10.4 Hz, $J_{H3H4a(trans)}$ 17.3 Hz, H_3), 5.24 (1H, ddd, J_{H4aH4b} 1.2 Hz, J_{H4aH2} 1.6 Hz, J_{H4aH3} 17.3 Hz, H_{4a}), 5.19 (1H, dt, J_{H4bH4a} 1.2 Hz, J_{H4bH2} 1.5 Hz, J_{H4bH3} 10.4 Hz, H_{4b}), 4.26-4.08 (1H, m, H_2), 3.68-3.6 (2H, br.m, H_{1a}, H_{1b}), 1.44 (9H, s, *t*-Bu); δ_C (50 MHz; $CDCl_3$, 25°C) 155.9 (C=O), 135.5 (C_3), 116.0 (C_4), 79.5 (Me_3CO), 64.7 (C_1), 54.5 (C_2), 28.2 (Me_3CO); m/z (FAB ms) 188 [(*M*+H)$^+$].

3.3.6. Cycloaddition Reactions of (4*R*)-3-(*N*-*t*-butoxycarbonyl)-2,2-dimethyl-4-vinyloxazolidine (**12**).

3.3.6.1. Cycloaddition Reaction with Benzonitrile Oxide: Preparation of

(5R,4'S)- and (5S,4'S)-3-*phenyl*-5-(3'-(N-t-*butoxycarbonyl*)-2',2'-*dimethyl*-*oxazolidin*-4'-*yl*)-2-*isoxazoline* **(19a)** and **(19b).**

To a stirred solution of benzohydroximoyl chloride (0.76 g, 4.9 mmol) and vinyl-oxazolidine **(12)** (1.0g, 4.4 mmol) in ether (30 ml) at room temperature was added over *ca.* 25 hours a solution of triethylamine (0.58 g, 5.8 mmol) in ether (30 ml). When the addition was complete, stirring was continued for 1 hour before filtering the reaction mixture through a pad of Celite and washing the filter cake through with ether (2 x 20 ml). The combined filtrate and washings were concentrated *in vacuo* and the residue flash column chromatographed (EtOAc/hexane, 1:19) affording a clear oil which solidified on standing to a white amorphous solid (^{1}H-NMR of the product showed it to be a 66:34 mixture of the title compounds) (1.29 g, 85%), (Found: $(M+H)^+$ 347.19705. $C_{19}H_{27}N_2O_4$ requires $(M+H)$, 347.19709.) $\nu_{max.}$ (neat) 1685 (C=O), 1595 cm^{-1} (C=N); δ_H (200 MHz; $CDCl_3$, 59°C) 7.63 (2H, br.s, ArH), 7.37-7.36 (3H, br.d, ArH) 5.2-5.0 and 4.87-4.67 (1H, 2br.m, H_5), 4.23-3.88 (3H, br.m, $H_{4'}$, $H_{5a'}$, $H_{5b'}$) 3.61-3.43 (1H, br.m, H_{4a}) 3.36-3.17 (1H, br.m, H_{4b}), 1.63, 1.59, 1.52, 1.48, and 1.44 (15H, 5s, $OC(CH_3)_2N$- and *t*-Bu); δ_C (90 MHz; $CDCl_3$) 156.9, 156.8 (C=O and C_3), 129.9, 128.5, 126.6 (PhCH), 129.6 (PhC), 94.2 ($C_{2'}$), 81.0, 80.5 (C_5), 80.4, 80.1 (Me_3CO), 65.1, 63.8 ($C_{5'}$), 59.3, 57.9 ($C_{4'}$), 37.5, 35.8 (C_4), 28.3, 28.2 (Me_3CO-), 27.3, 26.8 ($OC(CH_3)_2N$-); m/z (FAB ms) 347 [$(M+H)^+$].

3.3.6.2. Cycloaddition Reaction with ethoxycarbonylformonitrile oxide: Preparation of (5R,4'S)- and (5S,4'S)-3-*ethoxycarbonyl*-5-(3'-(N-t-*butoxycarbonyl*)-2',2'-*dimethyloxazolidin*-4-*yl*)-2-*isoxazoline* **(20a)** and **(20b).**

To a stirred solution of ethyl chloro-oximidoacetate (1.33 g, 8.8 mmol) and the vinyl-oxazolidine **(12)** (1.0 g, 4.4 mmol) in ether (25 ml) at room

temperature was added dropwise over *ca.* 24 hours a solution of triethylamine (1.07 g, 10.5 mmol) in ether (25 ml). When the addition was complete stirring was continued for 1 hour before filtering the reaction mixture through a pad of Celite and washing the filter cake with ether (2 x 20 ml). Concentration of the combined filtrate and washings *in vacuo* followed by flash column chromatography of the residue (Et_2O/hexane, 3:17 then 1:4) furnished the title compounds as a clear viscous oil which solidified on standing (68:32 mixture by ^{1}H-NMR) (1.34 g, 89%) (Found: C, 56.34; H, 7.37; N, 7.99. $C_{16}H_{26}N_2O_6$ requires C, 56.1; H, 7.65; N, 8.2%); $\nu_{max.}$ (neat) 1710 (br) (C=O), 1590 cm^{-1} (C=N); δ_H (200 MHz; $CDCl_3$, 53°C) 5.30-5.07 and 4.92-4.80 (1H, 2m, H_5), 4.33 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.05-3.86 (3H, m, $H_{4'}$, $H_{5a'}$, $H_{5b'}$), 3.48-3.08 (2H, m, H_{4a}, H_{4b}), 1.59, 1.56, 1.51, 1.49 (6H, 4s, $OC(CH_3)_2N$-), 1.48 (9H, s, *t*-Bu), 1.35 (3H, t, *J* 7.1 Hz, OCH_2CH_3); δ_C (50 MHz, $CDCl_3$, 58°C) 160.4 (C=O),152.0 (C_3), 94.4 ($C_{2'}$), 83.2, 82.5 (C_5), 80.8 (Me_3CO), 65.0, 63.6 ($C_{5'}$), 61.8 (OCH_2CH_3), 59.0, 57.5 ($C_{4'}$), 36.1, 34.7 (C_4), 28.2 (Me_3CO-), 27.3, 26.7, 23.9, ($OC(CH_3)_2N$-), 13.9 (OCH_2CH_3); m/z (FAB ms) 343 [(*M*+H)$^+$].

3.3.6.3. Cycloaddition Reaction with Bromonitrile Oxide: Preparation of (5*R*,4'*S*)- and (5*S*,4'*S*)-3-*bromo*-5-(3-(N-t-*butoxycarbonyl*)-2',2'-*dimethyloxazolidin*-4'-*yl*)-2-*isoxazoline* **(21a)** and **(21b).**

To a stirred solution of dibromoformaldoxime (1.78 g, 8.8 mmol) and the vinyl-oxazolidine **(12)** (1.0 g, 4.4 mmol) in ether (30 ml) was added over *ca.* 24 hours a solution of triethylamine (1.07 g, 10.56 mmol) in ether (25 ml). Stirring was continued for 1 hour after the addition was complete; the reaction mixture was then filtered through a pad of Celite and the filter cake washed with ether (2 x 20 ml). Concentration of the filtrate and

washings *in vacuo* followed by flash column chromatography of the residue furnished a mixture of the title adducts as a white amorphous solid (65:35 mixture by ^{1}H-NMR) (1.34 g, 87%) (Found: $(M+H)^+$ 349.07632. $C_{13}H_{22}N_2O_4$ requires $(M+H)$, 349.07634) $\nu_{max.}$ (neat) 1690 (C=O), 1580 cm^{-1} (C=N); δ_H (200 MHz; $CDCl_3$, 50°C) 5.15-4.95 (0.35H, br.m, H_5), 4.69-4.56 (0.65H, m, H_5), 4.16-3.83 (3H, m, $H_{4a'}$, $H_{5a'}$, $H_{5b'}$), 3.48 (0.65H, dd, J_{H4aH4b} 17.4 Hz, J_{H4aH5} 7.5 Hz, H_{4a}), 3.37 (0.35H, dd, J_{H4aH4b} 17.6 Hz, J_{H4aH5} 8.8 Hz, H_{4a}), 3.22-3.03 (1H, m, H_{4b}), 1.55, 1.52, 1.49 ($OC(CH_3)_2N$-), 1.46 (9H, s, *t*-Bu); δ_C (50 MHz; $CDCl_3$, 50°C) 153.0 (C=O), 137.6, 137.3 (C_3), 94.2 ($C_{2'}$), 81.6, 80.7 (C_5), 80.8 ($OCMe_3$), 64.9, 63.6 ($C_{5'}$), 58.9, 57.4 ($C_{4'}$), 44.0, 42.5 (C_4), 28.2 (Me_3CO-), 27.4, 26.7, 23.8, 23.1 ($OC(CH_3)_2N$-); m/z (FAB ms) 349 & 351 $[(M+H)^+]$.

3.3.7. Cycloaddition Reactions of (2*R*)-2-(*N*-*t*-butoxycarbonylamino)but-3-en-1-ol **(13)**.

3.3.7.1. Cycloaddition Reaction with Benzonitrile oxide: Preparation of (5R,2'S)- and (5S,2'S)-2'-(N-t-*butoxycarbonylamino*)-2'-(3-*phenyl*-2-*isoxazolin*-5-*yl*)*ethanol* **(22a)** and **(22b)**.

To a stirred solution of olefin **(13)** (0.1 g, 0.53 mmol) and benzohydroximoyl chloride (0.082 g, 0.53 mmol) in dichloromethane (5 ml) at room temperature was added a solution of triethylamine (0.061 g, 0.61 mmol) in dichloromethane (5 ml) over *ca* 16 hours. After stirring for a further 1 hour the reaction mixture was washed with water (2 x 20 ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Preparative tlc (EtOAc/hexane, 2:3) on 90% of the reaction mixture afforded two products (ratio, 40:60) which were in order of elution: **(22a)** which was isolated as a clear oil (0.041 g, 28%) $[\alpha]_D$ (20°C) -100.6° (c 0.8 in $CHCl_3$); δ_H (200

MHz; $CDCl_3$, 59°C) 7.69-7.60 (2H, m, ArH), 7.42-7.34 (3H, m, ArH), 5.17 (1H, br.d, NH), 4.82 (1H, dt, $J_{H5H2'}$ 6.9Hz, J_{H5H4a} 8.9 Hz, J_{H5H4b} 8.9Hz, H_5), 3.99-3.66 (3H, m, $H_{2'}$, $H_{1a'}$, $H_{1b'}$), 3.39 (2H, d, $J_{H4a/H4bH5}$ 8.9 Hz, H_{4a}, H_{4b}), 2.4 (1H, br.s, OH), 1.44 (9H, s, *t*-Bu); δ_C (50 MHz; $CDCl_3$) 157.1, 155.9 (C_3, C=O), 130.1,128.6, 126.7 (PhCH), 129.1 (PhC), 80.4 (C_5), 79.9 (Me_3CO), 61.5 ($C_{1'}$), 54.5 ($C_{2'}$), 37.8 (C_4), 28.2 (Me_3CO); m/z (FAB ms) 307 [(M+H)$^+$].

(22b) was isolated as a glassy solid (0.063 g, 43%) m.p. 115-117°C, $[\alpha]_D$ (20°C) +110.2° (c 1.3 in $CHCl_3$); δ_H (200 MHz; $CDCl_3$, 58°C) 7.66-7.6 (2H, m, ArH), 7.41-7.33 (3H, m, ArH), 4.97 (2H, ddd, $J_{H5H2'}$ 2.3 Hz J_{H5H4b} 8.7 Hz, J_{H5H4a} 10.3 Hz, H_5 and NH), 3.93-3.75 (3H, m, $H_{2'}$, $H_{1a'}$, $H_{1b'}$), 3.42 (1H, dd, J_{H4aH4b} 16.9 Hz, J_{H4aH5} 10.3 Hz, H_{4a}), 3.31 (1H, dd, J_{H4bH4a} 16.9 Hz, J_{H4bH5} 8.7 Hz, H_{4b}), 2.55 (1H, br.s, OH), 1.33 (9H, s, *t*-Bu); δ_C (50 MHz; $CDCl_3$) 157.4, 156.5 (C_3, C=O), 130.1, 128.6, 126.6 (PhCH), 129.0 (PhC), 80.5 (C_5), 79.8 (Me_3CO-), 63.2 ($C_{1'}$), 54.4 ($C_{2'}$), 37.6 (C_4), 28.0 (Me_3CO-).

3.3.7.2. Cycloaddition Reaction with Ethoxycarbonylformonitrile oxide: Preparation of (5R,2'S)- and (5S,2'S)-2'N-t-*butoxycarbonylamino*-2'-(3-*ethoxycarbonyl*-2-*isoxazolin*-5-*yl*)*ethanol* **(23a)** and **(23b)**.

To a stirred solution of the olefin **(13)** (0.1 g, 0.44 mmol) and ethyl chloro-oximidoacetate (0.08 g, 0.53 mmol) in dichloromethane (5 ml), at room temperature, was added over *ca* 16 hours a solution of triethylamine (0.062 g, 0.61 mmol) in dichloromethane (10 ml). When the addition was complete, tlc (EtOAc/hexane, 2:3) showed that the alkene had not been completely consumed. A further portion of ethyl chloro-oximidoacetate (0.07 g, 0.46 mmol) was added to the reaction mixture, followed by slow addition (*ca* 8 hours) of triethylamine (0.046 g, 0.46 mmol) in dichloromethane (5 ml). When the addition was complete the reaction

was stirred for 1 hour, then washed with water (2 x 20 ml), dried over $MgSO_4$ and the solvent evaporated *in vacuo* . Preparative tlc (EtOAc/ hexane, 2:3) on 90% of the crude product yielded three components. 3,4-di-ethoxycarbonylfuroxan (50 mg) (^{1}H-NMR spectrum consistent with a previous sample). (5R,2'S)-2'-N-t-*butoxycarbonylamino*-(3-*ethoxycarbonyl*-2-*isoxazolin*-5-*yl*)*ethanol* **(23a)** was isolated as a clear oil (0.05 g, 31%); $[\alpha]_D$ (20°C) -104.5° (c 1.15 in $CHCl_3$); $\nu_{max.}$ (neat) 3480 (O-H), 1720 (C=O), 1595 cm^{-1} (C=N); δ_H (200 MHz; $CDCl_3$) 5.23 (1H, br.d, NH), 4.87 (1H, dt, $J_{H5H2'}$ 7.6 Hz, J_{H5H4} 9.2 Hz, H_5), 4.31 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 3.89-3.65 (3H, br.m, $H_{2'}$, $H_{1a'}$, $H_{1b'}$), 3.23 (2H, d, J_{H4H5} 9.4 Hz, H_{4a}, H_{4b}), 2.95-2.50 (1H, br.s, OH), 1.41 (9H, s, *t*-Bu), 1.33 (3H, t, *J* 7.1 Hz, OCH_2CH_3); δ_C (50 MHz; $CDCl_3$) 160.5 (C=O), 156.0, 152.2 (C=O, C_3), 82.7 (C_5), 80.4 (Me_3CO), 62.2 ($C_{1'}$), 61.5 (OCH_2CH_3), 54.4 ($C_{2'}$), 36.6 (C_4), 28.4 (Me_3CO), 14.1 (OCH_2CH_3); m/z (FAB ms) 303 [(*M*+H)$^+$]. (5S,2'S)-2'-N-t-*butoxycarbonylamino*-(3-*ethoxycarbonyl*-2-*isoxazolin*-5-*yl*)*ethanol* **(23b)** was isolated as a clear oil (0.057 g, 36%); $[\alpha]_D$ (20°C) +150.3° (c 0.95 in $CHCl_3$); $\nu_{max.}$ (neat) 3360 (O-H), 1720 (C=O), 1595 cm^{-1} (C=N); δ_H (200 MHz; $CDCl_3$) 5.05 (1H, ddd, $J_{H5H2'}$ 2.0 Hz, J_{H5H4b} 9.1 Hz, J_{H5H4a} 11.1 Hz, H_5), 4.88 (1H, br.d, NH), 4.31 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 3.9-3.7 (3H, br.m, $H_{2'}$, $H_{1a'}$, $H_{1b'}$), 3.29 (1H, dd, J_{H4aH4b} 18.0 Hz, J_{H4aH5} 11.2 Hz, H_{4a}), 3.12 (1H, dd, J_{H4bH4a} 18.0 Hz, J_{H4bH5} 9.1 Hz, H_{4b}), 2.70 (1H, br.s, OH), 1.39 (9H, s, *t*-Bu), 1.33 (3H, t, *J* 7.1 Hz, OCH_2CH_3); δ_C (50 MHz; $CDCl_3$) 160.0 (C=O), 156.2, 152.3 (C=O, C_3), 82.7 (C_5), 80.1 (Me_3CO), 62.6 ($C_{1'}$), 61.9 (OCH_2CH_3), 54.2 ($C_{2'}$) 36.0 (C_4), 28.1 (Me_3CO), 13.9 (OCH_2CH_3); m/z (FAB ms) 303 [(*M*+H)$^+$].

3.3.8. Deprotection Reactions.

3.3.8.1. Reaction of (5*R*,4'*S*)- and (5*S*, 4'*S*)-3-phenyl-5-(3-*N*-*t*-butoxycarbonyl-2',2'-dimethyloxazolidin-4-yl)-2-isoxazoline **(19a)** and **(19b)** with TFA.

A solution of the cycloadduct mixture **(19a)** and **(19b)** (0.044 g, 0.13 mmol) in TFA/$H_2$0 (98:2) (1 ml) was stirred at room temperature for 10 minutes. The solvent was then evaporated *in vacuo* yielding a violet oil which was dissolved in dichloromethane (2 ml) and the solvent evaporated (x2). The residue was treated with saturated sodium carbonate solution (4 ml) and extracted with dichloromethane (3 x 10 ml). The combined organic extract was washed with brine (10 ml), dried over $MgSO_4$ and the solvent evaporated *in vacuo* to give a white solid (26 mg). Preparative tlc (EtOAc/MeOH/conc. ammonia, 85:10:5) furnished a mixture of (5R,2'S)- and (5S,2'S)-2'-*amino*-2'-(3-*phenyl*-2-*isoxazolin*-5-*yl*)*ethanol* **(25a)** and **(25b)** as a white solid (20 mg, 76%), δH (200 MHz; $CDCl_3$) 7.68-7.61 (4H, m, ArH)[1], 7.43-7.35 (6H, m, ArH)[1], 4.76-4.63 (2H, m, H_5)[1], 3.78-3.55 (4H, m, $H_{1a'}$, $H_{1b'}$)[1], 3.50-3.18 (4H), {3.43 (dd, J_{H4aH4b}16.7 Hz, J_{H4aH5} 10.6 Hz, H_{4a})[2], 3.35 (d, J_{H4bH5} 8.8 Hz, H_{4b})[3], 3.35 (d, J_{H4aH5} 10.3 Hz, H_{4a})[3], 3.24 (dd, J_{H4bH4a} 16.7 Hz, J_{H4bH5} 8.4 Hz, H_{4b})[2]}, 3.16-3.14 (1.4H, br.m, $H_{2'}$)[3], 3.0-2.9 (0.7H, br.s, $H_{2'}$)[2], 1.97 (6H, br.s, OH, NH_2)[1]; m/z (FAB ms) 207 [(*M*+H)$^+$].

1) both isomers. 2) minor (5*S*, 2'*S*)-isomer. 3) major (5*R*, 2'*S*)-isomer.

3.3.8.2. (5R,2'S)- and (5S,2'S)- 2'-N-t-*butoxycarbonylamino*-2'-(3-*phenyl*-2-*isoxazolin*-5-*yl*)*ethanol* **(22a)** and **(22b)**.

To a stirred solution of the mixture of (5*R*, 4'*S*)- and (5*S*, 4'*S*)-3-phenyl-5-(3'-*N*-*t*-butoxycarbonyl-2',2'-dimethyloxazolidin-4-yl)-2-isoxazoline **(19a)** and **(19b)** (1.08 g, 3.13 mmol) in methanol (30 ml) was added *p*-

toluenesulphonic acid (0.05 g, 0.26 mmol). This was stirred at room temperature for 68 hours, then concentrated *in vacuo* before adding water (30 ml) and extracting with ethyl acetate (3 x 50 ml). The combined organic extract was washed with 10% aqueous sodium carbonate (2 x 30 ml), water (50 ml) and dried over $MgSO_4$. Evaporation of the solvent *in vacuo*, followed by flash column chromatography (EtOAc/hexane, 3:7 then 2:3) furnished four compounds. Starting material **(19a)** and **(19b)** (0.135 g) identical by tlc and IR.

(5R,2'S)-2'-N-t-*butoxycarbonylamino*-2'-(3-*phenyl*-2-*isoxazolin*-5-*yl*)*ethanol* **(22a)** was isolated as a white solid (0.43 g, 45%)[1], m.p. 98-100°C (Found: $(M+H)^+$, 307.16579. $C_{16}H_{23}N_2O_4$ requires $(M+H)$, 307.16577); $[\alpha]_D$ (23°C) -82.2° (c 1.02 in $CHCl_3$); $\nu_{max.}$ (Nujol) 3520 (N-H), 3350 (O-H), 1680 cm^{-1} (C=O); δ_H (200 MHz; $CDCl_3$) 7.68-7.59 (2H, m, ArH), 7.43-7.34 (3H, m, ArH), 5.25 (1H, br.d, *J* 8.6 Hz, NH), 4.83 (1H, dt, J_{H5H4} 8.9 Hz, $J_{H5H2'}$ 7.2 Hz, H_5), 4.05-3.65 (3H, br.m, $H_{2'}$, $H_{1a'}$, $H_{1b'}$), 3.39 (2H, d, J_{H4H5} 9.2 Hz, H_{4a} & H_{4b}), 2.68 (1H, br.s, OH), 1.43 (9H, s, *t*-Bu); δ_C (50 MHz; $CDCl_3$) 157.1, 155.9 (C=O, C_3), 130.1, 128.6, 126.7 (PhCH), 129.1 (PhC), 80.5 (C_5), 80.0 ($OCMe_3$), 61.5 ($C_{1'}$), 54.5 ($C_{2'}$), 37.8 (C_4), 28.2 ($OCMe_3$); m/z (FAB ms) 307 $[(M+H)^+]$.

(5S,2'S)-2'-N-t-*butoxycarbonylamino*-2'-(3-*phenyl*-2-*isoxazolin*-5-*yl*)*ethanol* **(22b)** was isolated as a glassy solid (0.242 g, 25%)[2], m.p. 111-112.5°C (Found: $(M+H)^+$, 307.16578. $C_{16}H_{23}N_2O_4$ requires $(M+H)$, 307.16577); $[\alpha]_D$ (23°C) +104° (c 1.03 in $CHCl_3$); $\nu_{max.}$ (Nujol) 3380 (O-H, N-H), 1690 cm^{-1} (C=O); δ_H (200 MHz; $CDCl_3$) 7.68-7.61 (2H, m, ArH), 7.43-7.35 (3H, m, ArH), 4.99 (2H, NH and ddd, J_{H5H4a} 10.5 Hz, J_{H5H4b} 8.6 Hz, $J_{H5H2'}$ 2.0 Hz, H_5), 4.0-3.6 (3H, m, $H_{2'}$, $H_{1a'}$, $H_{1b'}$), 3.44 (1H, dd, J_{H4aH4b} 16.9 Hz, J_{H4aH5} 10.4 Hz, H_{4a}), 3.32 (1H, dd, J_{H4bH4a} 16.9 Hz, J_{H4bH5} 8.7 Hz,

H_{4b}), 2.50 (1H, br.s, OH), 1.32 (9H, s, *t*-Bu); δ_C (50 MHz; $CDCl_3$) 157.4, 156.5 (C=O, C_3), 130.2, 128.6, 126.6 (PhCH), 128.9 (PhC), 80.6 (C_5), 79.9 ($OCMe_3$), 63.3 ($C_{1'}$), 54.4 ($C_{2'}$), 37.6 (C_4), 28.0 ($OCMe_3$); m/z (FAB ms) 307 [(*M*+H)$^+$].

1) 51% based on recovered starting material.

2) 29% based on recovered starting material.

3.3.8.3. (5R,2'S)- and (5S,2'S)-2'-N-t-*butoxycarbonylamino*-2'-(3-*ethoxycarbonyl*-2-*isoxazolin*-5-*yl*)*ethanol* **(23a)** and **(23b).**

To a solution of the mixture of (5*R*,4'*S*)- and (5*S*,4'*S*)-3-ethoxycarbonyl-5-(3'-*N*-*t*-butoxycarbonyl-2',2'-dimethyloxazolidin-4-yl)-2-isoxazoline **(20a)** and **(20b)** (1.02 g, 2.98 mmol) in methanol (30 ml) was added *p*-toluenesulphonic acid (0.06g, 0.31 mmol). This was stirred at room temperature for 64 hours then concentrated *in vacuo*. The residue was diluted with water (30 ml) and extracted with ethyl acetate (3 x 30 ml). The combined organic extract was washed with 10% aqueous sodium carbonate (2 x 30 ml), brine (50 ml) then dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The residue was subjected to flash column chromatography (EtOAc/hexane, 3:7) (three columns were required to achieve complete separation of the diastereomeric alcohols) which yielded four compounds. Starting material **(20a)** and **(20b)** (0.21 g), IR identical to starting material, m/z (FAB ms) 343 [(*M*+H)$^+$].

(5R,2'S)-2'-N-t-*butoxycarbonylamino*-2'-(3-*ethoxycarbonyl*-2-*isoxazolin*-5-*yl*)*ethanol* **(23a)** was isolated as a clear oil (0.403 g, 45 mmol)[1], (Found: (*M*+H)$^+$, 303.15557. $C_{13}H_{23}N_2O_6$ requires (*M*+H), 303.15560); $[\alpha]_D$ (21°C) -114° (c 0.45 in $CHCl_3$); $\nu_{max.}$ (neat) 3380 (O-H), 1720 (br) (C=O ester & Boc), 1595 cm^{-1} (C=N); δ_H (200 MHz; $CDCl_3$) 5.15 (1H, br.d, NH), 5.09-4.83 (1H, m, H_5), 4.3 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 3.94-3.69

(3H, br.m, $H_{2'}$, $H_{1a'}$, $H_{1b'}$), 3.26 (2H, d, J_{H4H5} 9.2 Hz, H_{4a} & H_{4b}), 2.18 (1H, br.s, OH), 1.43 (9H, s, *t*-Bu), 1.35 (3H, t, *J* 7.1 Hz, OCH_2CH_3); δ_C (50 MHz; $CDCl_3$) 160.2 ($C{=}O_{ester}$), 155.7, 152.0 (C_3, $C{=}O_{Boc}$), 82.4 (C_5), 80.2 ($OCMe_3$), 62.0, 61.2 (OCH_2CH_3, $C_{1'}$), 54.0 ($C_{2'}$), 36.6 (C_4), 28.2 ($OCMe_3$), 13.9 (OCH_2CH_3).

(5S,2'S)-2'-N-t-*butoxycarbonylamino*-2'-(3-*ethoxycarbonyl*-2-*isoxazolin*-5-*yl*)*ethanol* **(23b)** was isolated as a clear oil (0.196 g, 22%)[2], (Found: (*M*+H)$^+$, 303.15559. $C_{13}H_{23}N_2O_6$ requires (*M*+H), 303.15560); $[\alpha]_D$ (21°C) +144° (c 0.5 in $CHCl_3$); $\nu_{max.}$ (neat) 3380 br (O-H), 1720 (br) (C=O ester & Boc), 1590 cm^{-1} (C=N); δ_H (200 MHz; $CDCl_3$) 5.05 (1H, ddd, J_{H5H4a} 11.2 Hz, J_{H5H4b} 9.1 Hz, $J_{H5H2'}$ 2.2 Hz, H_5), 4.85 (1H, br.d, NH), 4.32 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 3.88-3.71 (3H, m, $H_{2'}$, $H_{1a'}$, $H_{1b'}$), 3.31 (1H, dd, J_{H4aH4b} 18.0 Hz, J_{H4aH5} 11.2 Hz, H_{4a}), 3.14 (1H, dd, J_{H4bH4a} 18.0 Hz, J_{H4bH5} 9.1 Hz, H_{4b}), 2.40 (1H, br.s, OH), 1.41 (9H, s, *t*-Bu), 1.34 (3H, t, *J* 7.1 Hz, OCH_2CH_3); δ_C (50 MHz; $CDCl_3$) 160.1 ($C{=}O_{ester}$), 156.3, 152.4 (C_3, $C{=}O_{Boc}$), 82.8 (C_5), 80.2 ($OCMe_3$), 62.7, 62.0 (OCH_2CH_3, $C_{1'}$), 54.2 ($C_{2'}$), 36.1 (C_4), 28.1 ($OCMe_3$), 13.9 (OCH_2CH_3).

1) 56% based on recovered starting material.

2) 28% based on recovered starting material.

3.3.8.4. (5R,2S')- and (5S,2'S)-2'-N-t-*butoxycarbonylamino*-2'-(3-*bromo*-2-*isoxazolin*-5-*yl*)*ethanol* **(24a)** and **(24b)**.

A solution of the mixture of (5*R*,4'*S*)- and (5*S*,4'*S*)-3-bromo-5-(3'-*N*-*t*-butoxycarbonyl-2',2'-dimethyloxazolidin-4'-yl)-2-isoxazoline **(21a)** and **(21b)** (1.05 g, 3.01 mmol) and *p*-toluenesulphonic acid (0.069 g, 0.36 mmol) in methanol (20 ml) was stirred at room temperature for 90 hours. The reaction mixture was then concentrated *in vacuo*; the residue was

diluted with water and extracted with ethyl acetate (3 x 50 ml). The combined organic extract was washed with 10% aqueous sodium carbonate (2 x 30 ml), brine (50 ml), then dried over $MgSO_4$ and the solvent evaporated under reduced pressure. Flash column chromatography (EtOAc/hexane, 3:7) afforded four compounds.

Starting material **(21a)** and **(21b)** (0.17 g) (Identical to starting material by tlc and IR).

(5R,2'S)-2'-N-t-*butoxycarbonylamino*-2'-(3-*bromo*-2-*isoxazolin*-5-*yl*)*ethanol* **(24a)** was isolated as a clear oil which solidified on standing to give a white amorphous solid (0.392 g, 42%)[1], m.p. 108-109°C (fine white needles from hexane/toluene), (Found: (*M*+H)+, 309.04506. $C_{10}H_{18}BrN_2O_4$ requires (*M*+H), 309.04504); $[\alpha]_D$ (22°C) -82° (c 0.55 in CHCl3); $\nu_{max.}$ (neat) 3380 (br) (O-H), 1695 (C=O), 1585 cm^{-1} (w) (C=N); δ_H (200 MHz; $CDCl_3$) 5.16 (1H, br.d, *J* 8.9 Hz, NH), 4.75 (1H, dt, J_{H5H4} 9.1 Hz, $J_{H5H2'}$ 7.6 Hz, H_5), 3.94-3.71 (3H, m, $H_{2'}$, $H_{1a'}$, $H_{1b'}$), 3.29 (2H, d, J_{H4H5} 9.1 Hz, H_{4a} & H_{4b}), 2.41 (1H, br.s, OH), 1.44 (9H, s, *t*-Bu); δ_C (50 MHz; $CDCl_3$) 155.8 (C=O), 138.1 (C_3), 80.8 (C_5), 80.3 (O*C*Me_3), 61.2 ($C_{1'}$), 54.0 ($C_{2'}$), 44.3 (C_4), 28.2 (OC*Me*$_3$); m/z (FAB ms) 309 & 311 [(*M*+H)+].

(5S,2'S)-2'-N-t-*butoxycarbonylamino*-2'-(3-*bromo*-2-*isoxazolin*-5-*yl*)*ethanol* **(24b)** was isolated as a glassy solid which could not be recrystallised (0.198 g, 21%)[2], m.p. 99-101°C (after preparative tlc, EtOAc/hexane, 1:1); (Found: (*M*+H)+, 309.04506. $C_{10}H_{18}BrN_2O_4$ requires (*M*+H), 309.04504); $[\alpha]_D$ (22°C) +93.5° (c 1.5 in $CHCl_3$); $\nu_{max.}$ (neat) 3370 (br) (O-H), 1695 (C=O), 1595 cm^{-1} (w) (C=N); δ_H (200 MHz; $CDCl_3$) 4.94 (2H, NH and ddd, J_{H5H4a} 10.5 Hz, J_{H5H4b} 8.6 Hz, $J_{H5H2'}$ 1.9 Hz, H_5), 3.88-3.62 (3H, m, $H_{2'}$, $H_{1a'}$, $H_{1b'}$), 3.31 (1H, dd, J_{H4aH4b} 17.5 Hz, J_{H4aH5} 10.5 Hz, H_{4a}), 3.16 (1H, dd, J_{H4bH4a} 17.5 Hz, J_{H4bH5} 8.6 Hz, H_{4b}), 2.61 (1H, br.s,

OH), 1.43 (9H, s, *t*-Bu); δ_C (50 MHz, $CDCl_3$) 156.3 (C=O), 138.3 (C_3), 81.1 (C_5), 80.2 ($OCMe_3$), 62.6 ($C_{1'}$), 54.0 ($C_{2'}$), 43.9 (C_4), 28.1 ($OCMe_3$); m/z (FAB ms) 309 & 311 [(*M*+H)$^+$].

1) 51% based on recovered starting materials.

2) 25% based on recovered starting materials.

3.3.8.5. (5S, 2'S)-2'-*amino*-2'-(3-*phenyl*-2-*isoxazolin*-5-*yl*)*ethanol* (**25b**).

A solution of (5*S*,2'*S*)-2'-*N*-*t*-butoxycarbonylamino-2'-(3-phenyl-2-isoxazolin-5-yl)ethanol (**22b**) (0.08 g, 0.26 mmol) in TFA/H_2O (98:2, 1 ml) was stirred at room temperature for 1 hour. The solvent was then evaporated *in vacuo*, and dichloromethane (5 ml) added and evaporated. The residue was treated with saturated sodium carbonate solution (5 ml) and this extracted with dichloromethane (3 x 10 ml). The combined organic extract was washed with 10% aqueous sodium carbonate (20 ml), brine (20 ml), dried over $MgSO_4$ and the solvent evaporated under reduced pressure, to give a white solid (43 mg). Flash column chromatography (EtOAc/MeOH/conc. ammonia, 17:2:1) furnished a white solid (28 mg, 53%), m.p. 145-148°C (from hexane/toluene), (Found: (*M*+H)$^+$, 207.11335. $C_{11}H_{15}N_2O_2$ requires (*M*+H), 207.11334); $[\alpha]_D$ (22°C) +136.6° (c 0.5 in CH_2Cl_2); δH (200 MHz; $CDCl_3$) 7.69-7.62 (2H, m, ArH), 7.44-7.26 (3H, m, ArH), 4.47 (1H, br.s, H_5), 3.85-3.55 (2H, br.m, CH_2OH), 3.44 (1H, dd, J_{H4aH4b} 16.6 Hz, J_{H4aH5} 10.6 Hz, H_{4a}), 3.25 (1H, dd, J_{H4bH4a} 16.6 Hz, J_{H4bH5} 8.3 Hz, H_{4b}), 2.95 (1H, br.s, $H_{2'}$), 1.77 (*ca* 3H, br.s, OH, NH_2); m/z (FAB ms) 207 [(*M*+H)$^+$].

3.3.8.6. (5R,2'S)-2'-*amino*-2'-(3-*phenyl*-2-*isoxazolin*-5-*yl*)*ethanol* (**25a**).

A solution of (5R,2'S)-2'-*N*-*t*-butoxycarbonylamino-2'-(3-phenyl-2-isoxazolin-5-yl)ethanol (**22a**) in TFA/H_2O (98:2, 2 ml) was stirred at room

temperature for 30 minutes. The solvent was then evaporated *in vacuo* and dichloromethane (5 ml) added and evaporated. The residue was treated with saturated sodium carbonate solution (5 ml), and extracted into dichloromethane (3 x 10 ml). The combined organic extract was washed with 10% aqueous sodium carbonate (20 ml), brine (20 ml), dried over $MgSO_4$, and the solvent evaporated under reduced pressure. The resulting off-white solid was purified by preparative tlc (EtOAc/MeOH/conc. ammonia, 17:2:1) which furnished the title compound **(25a)** as a white solid (20 mg, 40%) m.p. 128-130°C dec. (from hexane/toluene), (Found: $(M+H)^+$, 207.11335. $C_{11}H_{15}N_2O_2$ requires $(M+H)$, 207.11334); $[\alpha]_D$ (20°C) -82°C (c 0.95 in CH_2Cl_2); δ_H (200 MHz; $CDCl_3$) 7.71-7.62 (2H, m, ArH), 7.43-7.36 (3H, m, ArH), 4.74-4.67 (1H, br.m, H_5), 3.79-3.55 (2H, br.m, CH_2OH), 3.36 (1H, d, J_{H4aH5} 9.8 Hz, H_{4a}), 3.36 (1H, d, J_{H4bH5} 9.3 Hz, H_{4b}), 3.18 (1H, br.s, $H_{2'}$), 1.91 (*ca* 3H, br.s, OH, NH_2); m/z (FAB ms) 207 $[(M+H)^+]$.

3.3.9. (5S,4'S)-3-*phenyl*-5-(2'-*phenyl*-4,5-*dihydro*-*oxazol*-4'-*yl*)-2-*isoxaz*-*oline* **(26b)**.

To a stirred solution of (5*S*,2'*S*)-2'-amino-2'-(3-phenyl-2-isoxazolin-5-yl)ethanol **(25b)** (7 mg, 0.034 mmol) in dichloromethane (1 ml), at room temperature was added a solution of ethyl benzimidate (7.3 mg, 0.05 mmol) in dichloromethane (0.5 ml). After 25 hours the solvent was evaporated *in vacuo* and the residue subjected to preparative tlc (EtOAc/hexane, 3:7) which furnished the title compound as a white solid (3 mg, 27 %), [a]$_D$ (21°C) +269° (c 0.075 in CHCl3); δ_H (360 MHz; $CDCl_3$) 7.91-7.89 (2H, m, ArH), 7.66-7.63 (2H, m, ArH), 7.40-7.35 (6H, m, ArH), 5.08 (1H, ddd, J_{H5H4a} 10.9 Hz, J_{H5H4b} 8.2 Hz, $J_{H5H4'}$ 3.8 Hz, $H_{5\ isoxaz.}$), 4.71 (1H, ddd, $J_{H4'H5a'}$ 9.9 Hz, $J_{H4'H5b'}$ 7.2 Hz, $J_{H4'H5}$ 3.8 Hz, $H_{4'\ oxaz.}$), 4.49 (1H,

dd, $J_{H5a'H4'}$ 9.9 Hz, $J_{H5a'H5b'}$ 9.0 Hz, $H_{5a'\ oxaz.}$), 4.41 (1H, dd, $J_{H5b'H5a'}$ 9.0 Hz, $J_{H5b'H4'}$ 7.2 Hz, $H_{5b'\ oxaz.}$), 3.39 (1H, dd, J_{H4aH4b} 16.9 Hz, J_{H4aH5} 10.9 Hz, $H_{4a\ isoxaz.}$), 3.30 (1H, dd, J_{H4bH4a} 16.9 Hz, J_{H4bH5} 8.2 Hz, $H_{4b\ isoxaz.}$).

3.4. Synthesis of 2-phenyl-4-vinyl-4,5-dihydro-oxazole (11)

3.4.1. Ethyl benzimidate hydrochloride.

A gentle stream of HCl gas was passed through a solution of benzonitrile (10 g, 97 mmol) in dry ether (15 ml) and dry ethanol (5 ml), cooled with an ice bath, until saturation was reached. The stoppered solution was stored in the fridge overnight, then concentrated *in vacuo* to give a white solid, which was washed with dry ether and dried *in vacuo,* furnishing the title compound as a white powder (14.95 g, 83%), m.p. 118°C (dec) (lit.,[150] 119-120°C).

3.4.2. (*S*)-serine methyl ester hydrochloride (15).

Thionyl chloride (275 ml, 448 g, 3.8 mol) was added, with stirring, to methanol (HPLC grade, 1000 ml), which had been cooled to -25°C, at such a rate that the temperature did not exceed -20°C. (*S*)-serine (111.3 g, 1.06 mol) was added in small portions. The reaction mixture was allowed to warm to room temperature and stirring continued overnight. The resulting white solid was filtered off and the filtrate concentrated *in vacuo* to afford a second crop of the product. The combined solids were washed with ether, dried under suction and recrystallised from propan-1-ol to yield the title compound as a white crystalline solid (136 g, 82 %), m.p. 153.5-156°C (dec.) (lit.,[151] 167°C), $\nu_{max.}$ (Nujol) 3350 (O-H), 1750 cm^{-1} (C=O); δ_H (200 MHz; CD_3OD) 5.05 (4H, br.s, OH, NH_3^+), 4.29 (1H, t, J_{H2H3} 4.0 Hz, H_2), 4.11 (1H, d, J_{H3aH2} 4.0 Hz, H_{3a}), 4.10 (1H, d, J_{H3bH2} 4.1 Hz, H_{3b}), 3.95 (3H, s, OCH_3).

3.4.3. (4*S*)-4-methoxycarbonyl-2-phenyl-4,5-dihydro-oxazole (**29**).

The title compound was prepared by the procedure described by Tkaczuk and Thornton.[107]

To a solution of (*S*)-serine methyl ester hydrochloride (**15**) (4.6 g, 29.5 mmol) in water (3 ml) was added a solution of ethyl benzimidate (8.2 g, 44 mmol) in dichloromethane (18 ml). The flask was firmly stoppered and shaken for 2 days; the reaction mixture was then filtered through Celite, and the filter cake washed through with dichloromethane (2 x 30 ml). The filtrate was washed with water (50 ml), dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The resulting oil was subjected to flash column chromatography (Et_2O/hexane, 1:3) which furnished the title compound (**29**) as a clear oil (4.36 g, 72%) (in larger scale preparations the product can be separated from the excess ethyl benzimidate by vacuum distillation. The starting material distilled at 47°C (0.09 mmHg) and the product came over at 120°C (0.09mmHg)). $\nu_{max.}$ (neat) 1740 (C=O), 1640 cm^{-1} (C=N); δ_H (200 MHz; $CDCl_3$), 7.96-7.91 (2H, m, ArH), 7.44-7.31 (3H, m, ArH), 4.90 (1H, dd, J_{H4H5a} 10.6 Hz, J_{H4H5b} 7.8 Hz, H_4), 4.64 (1H, dd, J_{H5bH5a} 8.6 Hz, J_{H5bH4} 7.8 Hz, H_{4b}), 4.52 (1H, dd, J_{H5aH5b} 8.6 Hz, J_{H5aH4} 10.6 Hz, H_{5a}), 3.76 (3H, s, OCH_3); δ_C (50 MHz; $CDCl_3$) 171.3 (C=O), 166.0 (C_2), 131.6, 128.3, 128.1 (PhCH), 126.7 (PhC), 69.3, 68.4 (C_4, C_5), 52.4 (OCH_3); m/z 205 (*M*+, 8%), 146 (100), 118 (16), 105 (11), 91 (27), 77 (16).

3.4.4. Attempted preparation of (4*S*)-4-formyl-2-phenyl-4,5-dihydro-oxazole (**27**).

This reaction was carried out according to the procedure described by Tkaczuk and Thornton.[107]

To a cooled (-78°C) stirred solution of 4-methoxycarbonyl-2-phenyl-4,5-dihydro-oxazole (**29**) (0.209 g, 1.02 mmol) in dry dichloromethane (8ml),

under a nitrogen atmosphere, was added a solution of DIBAL (1M in hexanes, 1.02 ml, 1.02 mmol) at such a rate that the temperature did not exceed -70°C. After stirring for 3 hours methanol (0.4 ml) was added and stirring continued for 30 minutes. Chloroform (5 ml) and saturated sodium potassium tartrate (15 ml) were added and the reaction mixture allowed to warm to room temperature; the organic layer was separated and the aqueous phase extracted with chloroform (3 x 25 ml). The combined organic extracts were dried over $MgSO_4$ and the solvent evaporated *in vacuo*. δ_H (60 MHz; $CDCl_3$) 9.8 (s, CHO), 3.7 (s, OCH3). ^{1}H-NMR showed that there had been about 20% conversion to the desired aldehyde, the reaction was taken no further in the light of the reported instability of **(27)**. Attempts to vary conditions : solvent (toluene), quantity of DIBAL, and temperature proved fruitless.

3.4.5. (4*R*)-4-hydroxymethyl-2-phenyl-4,5-dihydro-oxazole **(30)**.

The title alcohol was prepared by the literature procedure[110] with some modifications.

To a stirred suspension of lithium aluminium hydride (9.86 g, 260 mmol) in dry ether (500 ml) at 0°C, under an argon atmosphere, was added as rapidly as possible a solution of (4*S*)-4-methoxycarbonyl-2-phenyl-4,5-dihydro-oxazole **(29)** (26.6 g, 130 mmol) in dry ether (50 ml). After stirring for 2 minutes the reaction was quenched with water (10 ml), 20% aqueous sodium hydroxide solution (7.4 ml) and finally water (50 ml). After stirring overnight the granular precipitate which had formed was filtered and washed with several portions of ether. The combined filtrate and washings were concentrated *in vacuo* to approximately 50 ml, and the precipitated white solid filtered off, dissolved in dichloromethane and dried over $MgSO_4$. Evaporation of the solvent afforded a white solid which

was recrystallised from cyclohexane to yield a fluffy white solid (15.92 g, 70%), m.p. 92-96°C (lit.,[110] 99.5°C) (Found: *M*+, 177.0794. Calc. for $C_{10}H_{11}NO_2$ *M*, 177.07897); $[\alpha]_D$ (20°C) +81° (c 1.0 in $CHCl_3$); $\nu_{max.}$ (Nujol) 3350 br (O-H), 1640 cm^{-1} (C=N); δ_H (200 MHz; $CDCl_3$) 7.78-7.72 (2H, m, ArH), 7.42-7.22 (3H, m, ArH), 4.5-3.5 (6H, m, H_4, H_{5a}, H_{5b}, HOCH_2); δ_C (50 MHz; $CDCl_3$) 165.3 (C_2), 131.2, 128.0 (PhCH), 126.8 (PhC), 69.0, 67.9 (C_5, $HOCH_2$), 63.3 (C_4); m/z 177 (*M*+, 5%), 146 (100), 118 (15), 105 (17), 77 (22).

3.4.6. Attempts to oxidise (4*R*)-4-hydroxymethyl-2-phenyl-4,5-dihydro-oxazole (**30**) to (4*S*)- 4-formyl-2-phenyl-4,5-dihydro-oxazole (**27**).

3.4.6.1. Oxidation with pyridinium chlorochromate.[111]

Pyridinium chlorochromate (0.24 g, 1.12 mmol) was suspended in dry dichloromethane (2 ml) and a solution of the alcohol (0.1 g, 0.56 mmol) (**30**) in dichloromethane (1 ml) added. After stirring for 3 hours tlc (Et_2O/hexane, 1:1) showed unconsumed alcohol. A further equivalent of pyridinium chlorochromate was added and stirring continued for 2 hours. The reaction mixture was diluted with dry ether (15 ml), and the supernatant liquid decanted off. The residual brown sludge was washed with ether (4 x 10 ml), and the combined organic extract filtered through a silica pad and then concentrated *in vacuo*. ^{1}H-NMR (60 MHz) of the crude product showed no aldehyde signal between 9 and 10 ppm, so the reaction was taken no further.

3.4.6.2. Swern Oxidation.[112]

A solution of oxalyl chloride (78 mg, 0.61 mmol) in dry dichloromethane (1.2 ml) was cooled to -60°C under a nitrogen atmosphere, and dry

DMSO (94 mg, 1.22 mmol) in dry dichloromethane (0.5 ml) added dropwise over 5 minutes. After stirring for a further 10 minutes a solution of the alcohol **(30)** (104 mg, 0.56 mmol) in dry dichloromethane (0.6 ml) was added dropwise over 5 minutes. Stirring was continued for 15 minutes, then triethylamine (280 mg, 2.78 mmol) was added dropwise over 5 minutes. The cooling was then removed and the reaction allowed to warm to room temperature (the solution changed from being clear and colourless to a clear yellow colour on warming); water (1.6 ml) was added and after 10 minutes the organic layer was separated. The aqueous phase was extracted with dichloromethane (20 ml) and the combined organic extract washed successively with dilute HCl, water, sodium carbonate solution and water, then dried over $MgSO_4$ and the solvent evaporated *in vacuo*. ^{1}H-NMR (60 MHz) of the crude product showed only a trace of aldehyde (which is reported to be unstable at room temperature)[107] so the reaction was taken no further.

3.4.7. *(4S)-4-hydroxymethyl-2-phenyl-4,5-dihydro-oxazole-O-p-toluene sulphonate* **(31)**.

A solution of alcohol **(30)** (5.3 g, 30 mmol) and *p*-toluenesulphonyl chloride (8.2 g, 43 mmol) in dry pyridine was stirred for 16 hours at room temperature. The reaction mixture was then concentated *in vacuo*, and the residue partitioned between ethyl acetate and water. The aqueous layer was extracted with two more portions of ethyl acetate (2 x 50 ml) and the combined organic extract washed with water (2 x 180 ml), then dried over $MgSO_4$ and the solvent evaporated *in vacuo*. Flash column chromatography (Gradient; hexane to EtOAc/hexane 2:3) furnished two products: unidentified white solid (3.52 g) m.p. 109-111°C δ_H (200 MHz; $CDCl_3$) 7.79-7.74 (2H, m, ArH), 7.55-7.37 (3H, m, ArH), 6.62 (1H, br.s),

4.72-4.61 (1H, m), 3.91 (2H, dd, *J*11.2 and 4.3 Hz), 3.74 (2H, dd, *J* 11.2 and 6.2 Hz); δ_C (50 MHz; $CDCl_3$) 167.0 (q), 133.4 (PhC), 131.9, 128.5, 126.9 (PhCH), 50.8 (CH), 43.5 (CH_2);

The minor component, tosylate (**31**), was isolated as a white solid (0.263 g, 3%), m.p. 107-111°C (from cyclohexane) (Found: (*M*+H)$^+$, 332.09567. $C_{17}H_{18}NO_4S$ requires (*M*+H), 332.09565); $[\alpha]_D$ (20°C) +34° (c 0.95 in CH_2Cl_2); δ_H (200 MHz; $CDCl_3$) 7.86-7.72 (2H, m, ArH), 7.50-7.24 (3H, m, ArH), 4.53-4.21 (4H, m, H_4, TsOC*H*$_2$, H_{5a}), 4.07-3.99 (1H, m, H_{5b}), 2.39 (3H, s, CH_3); δ_C (50 MHz; $CDCl_3$) 165.7 (C_2), 144.8, 132.5, 126.9 (PhC), 131.6, 129.7, 128.5, 128.2, 128.1, 127.8 (PhCH), 70.6, 69.6 (TsO*C*H$_2$, C_5), 65.0 (C_4); m/z (FAB ms) 332 [(*M*+H)$^+$].

3.4.8. (R/S)-4-*bromomethyl*-2-*phenyl*-4,5-*dihydro*-*oxazole* (**32**).

To a stirred solution of thionyl bromide (14.08 g, 5.25 ml, 67.8 mmol) in dry toluene (40 ml) at 0°C was added a solution of (*R*)-4-hydroxymethyl-2-phenyl-4,5-dihydro-oxazole (**30**) (3.0 g, 16.9 mmol) in dry toluene (20 ml). The reaction mixture was allowed to warm to room temperature, and stirring continued for 8 hours before quenching with saturated aqueous sodium hydrogen carbonate until the solution was basic. The mixture was poured into water (50 ml) and the organic layer separated; the aqueous portion was extracted with ethyl acetate (2 x 50 ml). The combined organic extract was dried over $MgSO_4$ and then the solvent evaporated *in vacuo* to yield a brown oil, which solidified on standing. Kugelrohr distillation (100°C, 0.007mmHg) afforded a white solid (2.76 g, 68%) from which an analytical sample was obtained by recrystallisation from di-isopropyl ether, m.p. 70-71.5°C (Found: C, 50.0; H, 4.42; N, 5.8. $C_{10}H_{10}BrNO$ requires C, 50.02; H, 4.20; N, 5.83%); $\nu_{max.}$ (Nujol) 1640

cm^{-1} (C=N); δ_H (200 MHz; $CDCl_3$) 7.97-7.91 (2H, m, ArH), 7.54-7.36 (3H, m, ArH), 4.60 (1H, dddd, J_{H4H5b} 9.2 Hz, J_{H4H5a} 6.7 Hz, $J_{H4H4\alpha}$ 7.5 and 3.6 Hz, H_4), 4.51 (1H, t, J_{H5bH5a} 8.6 Hz, J_{H5bH4} 9.2 Hz, H_{5b}), 4.34 (1H, dd, J_{H5aH5b} 8.5 Hz, J_{H5aH4} 6.7 Hz, H_{5a}), 3.67 (1H, dd, $J_{H4\alpha H4\alpha}$ 10.1 Hz, $J_{H4\alpha H4}$ 3.6 Hz, BrCH*H*), 3.40 (1H, dd, $J_{H4\alpha H4\alpha}$ 10.1 Hz, $J_{H4\alpha H4}$ 7.6 Hz, BrC*H*H); δ_C (50 MHz; $CDCl_3$) 165.5 (C_2), 131.6, 128.3 (PhCH), 127.1 (PhC), 71.5 (C_5), 67.1 (C_4), 35.4 ($BrCH_2$); m/z (FAB ms), 242 [(*M*+H)$^+$].

3.4.9. (R/S)-4-*iodomethyl*-2-*phenyl*-4,5-*dihydro-oxazole* (**34**).

To a solution of sodium iodide (3.12 g, 20.8 mmol) in acetone (20 ml) was added a solution of (*R/S*)-4-bromomethyl-2-phenyl-4,5-dihydro-oxazole (**32**) (1.0 g, 4.17 mmol) in acetone (10 ml). After refluxing for 7 hours the reaction was allowed to cool and the solvent evaporated *in vacuo*. The residue was partitioned between water and ethyl acetate; the aqueous layer was extracted with ethyl acetate (2 x 40 ml). The combined organic extract was washed with 10% aqueous sodium metabisulphite (50 ml) then dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The residual brown oil was subjected to flash column chromatography (Et_2O/hexane, 1:1) which yielded a pale yellow solid (0.99 g, 83%), m.p. 72-73°C (Kugelrohr distillation of this material (150°C, 0.1 mmHg) afforded a sample of m.p. 73.5-74.5°C); (Found: (*M*+H)$^+$, 287.98873. $C_{10}H_{11}INO$ requires (*M*+H), 287.98872); $\nu_{max.}$ (Nujol) 1640 cm^{-1} (C=N); δ_H (200 MHz; C_6D_6) 8.19-8.10 (2H, m, ArH), 7.16-7.01 (3H, m, ArH), 4.04-3.90 (1H, m, H_4), 3.80 (1H, t, J_{H5aH5b} 8.6 Hz, J_{H5aH4} 9.1 Hz, H_{5a}), 3.68 (1H, dd, J_{H5bH5a} 8.6 Hz, J_{H5bH4} 7.3 Hz, H_{5b}), 2.91 (1H, dd, $J_{H4\alpha H4\alpha}$ 10.0 Hz, $J_{H4\alpha H4}$ 4.0 Hz, ICH*H*), 2.76 (1H, dd, $J_{H4\alpha H4\alpha}$ 9.9 Hz, $J_{H4\alpha H4}$ 7.1 Hz, IC*H*H); δ_C (50 MHz; $CDCl_3$) 164.8 (C_2), 131.4, 128.1 (PhCH), 127.0 (PhC),

72.8 (C_5), 66.9 (C_4), 10.5 (ICH_2).

3.4.10. Preparation of (2-phenyl-4,5-dihydro-oxazol-4-yl)methyl triphenylphosphonium halides.

3.4.10.1. Attempted Preparation of (2-phenyl-4,5-dihydro-oxazol-4-yl)methyl triphenylphosphonium bromide (33).

To a stirred solution of triphenylphosphine (0.115 g, 0.44 mmol) in benzene (1 ml) at room temperature was added a solution of 4-bromomethyl-2-phenyl-4,5-dihydro-oxazole **(32)** (0.10 g, 0.42 mmol) in benzene (1 ml). The reaction was stirred at 40°C for 10 hours, at which time tlc (Et_2O/light petrol, 7:3) showed no product formation. Stirring under reflux for 24 hours also failed to produce any of the desired phosphonium salt (tlc). The benzene was evaporated *in vacuo* and replaced with dry ethanol (2 ml), after stirring under reflux for 48 hours tlc again indicated no product formation.

3.4.10.2. *(4R/S)-(2-phenyl-4,5-dihydro-oxazol-4-yl)methyl triphenyl-phosphonium iodide* (33).

A solution of 4-iodomethyl-2-phenyl-4,5-dihydro-oxazole **(34)** (10.77 g, 37.5 mmol) and triphenylphosphine (12.63 g, 48 mmol) in dry toluene was stirred under reflux for 48 hours. After cooling to room temperature the precipitated phosphonium salt was filtered off, washed with toluene and dried *in vacuo*. The resulting yellowish powder was vigorously stirred in refluxing ether for 5 minutes, then filtered, and washed with several portions of the same solvent. The product was obtained, after drying *in vacuo,* as a white powder (18.66 g, 91%), m.p. 194-196°C (Found: M^+, 422.16736. $C_{28}H_{25}NOP$ requires *M*, 422.16737); δ_H (200 MHz, CD_3OD) 8.07-7.38 (20H, m, ArH), 4.74-4.55 (3H, m, H_4, H_{5a}, H_{5b}), 4.09-3.97 (2H,

m, Ph_3PCH_2); δ_C (50 MHz, CD_3OD) 164.1 (C_2), 134.04, 133.98, 133.3, 133.1131.1, 129.4, 129.2, 127.5, 126.0, 119.6, 117.8 (PhC & PhCH), 72.6 (C_4, J_{C4P} 16.4 Hz), 60.7 (C_5, J_{C5P} 5.0 Hz), 28.4 (Ph_3PCH_2, J_{CH2P} 53.4 Hz); m/z (FAB ms) 422 $[(M^+]-I^-$.

3.4.11. 4-(R/S)-2-*phenyl*-4-*vinyl*-4,5-*dihydro-oxazole* (**11**).

3.4.11.1. Wittig Reaction with butyllithium as the base.

To a stirred suspension of the phosphonium iodide (**33**) (2.5 g, 4.55 mmol) in dry THF (25 ml) under a nitrogen atmosphere and cooled to *ca.* -78°C was added *n*-butyllithium (1.6 M, 2.94 ml, 4.7 mmol). This was stirred for 30 minutes, and then allowed to warm to room temperature before passing gaseous formaldehyde in a stream of nitrogen onto the surface of the ylide solution. When the red colour of the ylide had completely disappeared the resulting yellow solution was stirred at room temperature for 30 minutes and then refluxed for 2 hours. After cooling the solvent was evaporated *in vacuo*; the residue was poured into water and extracted with ethyl acetate (3 x 40 ml). The combine organic extract was dried over $MgSO_4$ and the solvent removed under reduced pressure. Flash column chromatography of the residue (EtOAc/hexane, 1:9) furnished the title compound (**11**) as a clear oil (0.4 g, 51%), (Found: $(M+H)^+$, 174.091884. $C_{11}H_{12}NO$ requires (*M*+H), 174.09188); δ_H (200 MHz; $CDCl_3$) 7.99-7.94 (2H, m, ArH), 7.52-7.25 (3H, m, ArH), 5.91 (1H, ddd, $J_{H1'H2b'}$ 17.1 Hz, $J_{H1'H2a'}$ 10.1 Hz, $J_{H1'H4}$ 7.1 Hz, $H_2C=CH$-), 5.32 (1H, ddd, $J_{H2b'H1'}$ 17.1 Hz, $J_{H2b'H2a'}$ 1.4 Hz, $J_{H2b'H4}$ 1.2 Hz, H*H*C=CH-), 5.20 (1H, ddd, $J_{H2a'H1'}$ 10.1 Hz, $J_{H2a'H2b'}$ 1.4 Hz, $J_{H2b'H4}$ 0.9 Hz, *H*HC=CH-), 4.81 (1H, m, J_{H4H5a} 9.8 Hz, J_{H4H5b} 8.2 Hz, $J_{H4H1'}$ 7.1 Hz, $J_{H4H2b'}$ 1.2 Hz, $J_{H4H2a'}$ 0.9 Hz, H_4), 4.56 (1H, dd, J_{H5aH4} 9.8 Hz, J_{H5aH5b} 8.2 Hz, H_{5a}). 4.13 (1H, t, J_{H5bH5a}

8.2 Hz, J_{H5bH4} 8.2 Hz, H_{5b}); δ_C(50 MHz; $CDCl_3$) 164.3 (C_2), 137.8 ($C_{1'}$), 131.3, 128.2 (PhCH), 127.4 (PhC), 116.7 ($C_{2'}$), 72.2 (C_5), 68.7 (C_4); m/z (FAB ms) 174 [(*M*+H)$^+$].

3.4.11.2. Using potassium-*t*-butoxide as the base.

To a stirred suspension of the phosphonium iodide **(33)** (2.0 g, 3.64 mmol) in dry THF (20 ml) was added a solution of potassium-*t*-butoxide (0.41 g, 3.64 mmol) in dry THF (10 ml). After stirring for three hours at room temperature a stream of formaldehyde in nitrogen was passed onto the surface of the ylide solution until the bright yellow colour had disappeared. The reaction mixture was refluxed for 1 hour before cooling, adding water (50 ml) and extracting with ethyl acetate (3 x 50 ml). The combined organic extract was washed with water (50 ml), brine (50 ml) and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* followed by flash column chromatography on the residue (EtOAc/hexane, 3:17) furnished the desired olefin **(11)** as a clear oil (0.267 g, 42%).

3.4.11.3. Using potassium carbonate as the base.

To a stirred solution of the phosphonium iodide **(33)** (1.0 g, 1.82 mmol) and potassium carbonate (0.25 g, 1.82 mmol) in dry THF (20 ml) was added an excess of formaldehyde (estimated) (passed in on a stream of nitrogen) followed by 18-crown-6 (10 mg). The mixture was refluxed for 18 hours, then cooled and the solvent evaporated *in vacuo*. The residue was dissolved in ether (50 ml) and filtered through a pad of silica; the silica was washed through with several portions of ether. The combined filtrate and washings were evaporated under reduced pressure furnishing the alkene **(11)** as a clear oil (80 mg, 26%).

3.5. Cycloaddition Reactions of 4-(*R/S*)-2-phenyl-4-vinyl-4,5-dihydro-oxazole (11).

3.5.1. With ethoxycarbonylformonitrile oxide.

To a stirred solution of alkene (**11**) (0.1 g, 0.58 mmol) and ethyl chloro-oximidoacetate (0.135 g, 0.87 mmol) in ether (2 ml) was added a solution of triethylamine (0.105 g, 1.04 mmol) in ether (6 ml) over 21 hours. Tlc (EtOAc/hexane, 1:3) of the reaction mixture showed that there was a considerable amount of unconsumed alkene. A second portion of ethyl chloro-oximidoacetate (0.087 g, 0.58 mmol) in ether (3 ml) was added followed by addition of a solution of triethylamine (0.059 g, 0.58 mmol) in ether (3 ml) over 10 hours. The reaction mixture was filtered through Celite, and the filter cake washed through with ethyl acetate. The combined filtrate and washings were concentrated *in vacuo*. Half of the crude product was set aside, the other half was subjected to preparative tlc (EtOAc/hexane, 3:7) eluting each plate twice. Three components were isolated.

4,5-diethoxycarbonylfurazan-*N*-oxide was isolated as a clear oil (20 mg) δ_H (80 MHz; $CDCl_3$) 4.47 (2H, q, *J* 7.1 Hz OCH_2CH_3), 4.42 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 1.40 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.36 (3H, t, *J* 7.1 Hz, OCH_2CH_3).

(RS/S R)-3-*ethoxycarbonyl*-5-(2-*phenyl*-4,5-*dihydro-oxazol*-4-*yl*)-2-*isoxazoline* (**36a**) was isolated as a white solid (86 mg, 51.5%), m.p.101-102°C (Found: $(M+H)^+$ 289.11880. $C_{15}H_{17}N_2O_4$ requires 289.11882); δ_H (200 MHz; C_6D_6) 8.14-8.09 (2H, m, ArH), 7.16-7.03 (3H, m, ArH), 4.23-4.10 (1H, m, $H_{5\ isoxaz.}$), 3.98 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 3.93-3.83 (3H, m, $H_{4'}$, $H_{5a'}$, $H_{5b'\ oxaz.}$), 3.18 (1H, dd, J_{H4aH4b} 17.9 Hz, J_{H4aH5} 7.1 Hz, $H_{4a\ isoxaz.}$), 2.83 (1H, dd, J_{H4bH4a} 17.9 Hz, J_{H4bH5} 10.9 Hz, $H_{4b\ isoxaz.}$), 0.94 (3H, t, *J* 7.1 Hz, OCH_2CH_3); δ_C (50 MHz; C_6D_6) 165.4 ($C_{2'\ oxaz.}$), 160.7 (C=O),

151.9 ($C_{3\ isoxaz.}$), 131.6 (PhCH)[1], 85.2 ($C_{5\ isoxaz.}$), 70.3, 69.9 (C_5 & $C_{4\ oxaz.}$), 61.6 (OCH_2CH_3), 37.6 ($C_{4\ isoxaz.}$), 14.0 (OCH_2CH_3); m/z (FAB ms) 289 [$(M+H)^+$].

(RR/SS)-3-*ethoxycarbonyl*-5-(2-*phenyl*-4,5-*dihydro-oxazol*-4-*yl*)-2-*isoxazoline* **(36b)**. was isolated as a clear oil (22 mg, 13 %); δ_H (360 MHz; C_6D_6) 8.10-8.06 (2H, m, ArH), 7.07-6.98 (3H, m, ArH), 4.27 (1H, ddd, J_{H5H4a} 8.0 Hz, J_{H5H4b} 11.6 Hz, $J_{H5H4'}$ 3.4 Hz, $H_{5\ isoxaz.}$), 3.99 (1H, dd, $J_{H5a'H5b'}$ 8.1 Hz, $J_{H5a'H4'}$ 7.3 Hz, $H_{5a'\ oxaz.}$), 3.96-3.86 (3H, m, OCH_2CH_3, $C_{4'\ oxaz.}$), 3.76 (1H, dd, $J_{H5b'H5a'}$ 8.1 Hz, $J_{H5b'H4'}$ 9.9 Hz, $H_{5b'\ oxaz.}$), 3.21 (1H, dd, J_{H4aH4b} 17.5 Hz, J_{H4aH5} 8.0 Hz, $H_{4a\ isoxaz.}$), 2.72 (1H, dd, J_{H4bH4a} 17.5 Hz, J_{H4bH5} 11.6 Hz, $H_{4b\ isoxaz.}$), 0.89 (3H, t, J 7.1 Hz, OCH_2CH_3).

HPLC analysis of the reaction mixture (reverse phase column, eluted with H_2O/MeOH, 2:3) gave an isomer ratio (36a:36b) of 82:18.

1) Other phenyl signals are masked by the solvent peak.

3.5.2. With benzonitrile oxide.

To a stirred solution of alkene **(11)** (0.10 g, 0.58 mmol) and benzohydroximoyl chloride (0.101 g, 0.65 mmol) in ether (5 ml), at room temperature, was added a solution of triethylamine (0.07 g, 0.7 mmol) in ether (5 ml) over 15 hours. When the addition was complete, stirring was continued for a further hour before filtering the reaction mixture through a pad of Celite; the filter cake was washed through with several portions of ether. The combined filtrate and washings was concentrated *in vacuo* and half of the crude product set aside; the remainder was subjected to preparative tlc (EtOAc/hexane, 1:1) which furnished two isomeric products with an isolated ratio of 70:30.

(RS/SR)-3-*phenyl*-5-(2-*phenyl*-4,5-*dihydro-oxazole*-4-*yl*)-2-*isoxazoline* **(26a)** was isolated as a crystalline solid (51 mg, 60%), m.p. 126-127°C

(from hexane/ether), (Found: $(M+H)^+$, 293.12898. $C_{18}H_{16}N_2O_2$ requires 293.12899); δ_H (360 MHz; $CDCl_3$) 7.99-7.95 (2H, m, ArH), 7.59-7.54 (2H, m, ArH), 7.27-7.15 (6H, m, ArH), 4.37 (1H, ddd, J_{H5H4b} 6.4 Hz, $J_{H5H4'}$ 8.4 Hz, J_{H5H4a} 10.3 Hz, $H_{5\ isoxaz.}$), 4.28-4.08 (2H, m, $H_{4'}$& $H_{5a'\ oxaz.}$), 4.13 (1H, t, $J_{H5b'H5a'}$ 8.3 Hz, $J_{H5b'H4'}$ 7.9 Hz, $H_{5b'\ oxaz.}$), 3.30 (1H, dd, J_{H4aH4b} 17.0 Hz, J_{H4aH5} 6.4 Hz, $H_{4a\ isoxaz.}$), 3.13 (1H, dd, J_{H4bH4a} 17.0 Hz, J_{H4bH5} 10.3 Hz, $H_{4b\ isoxaz.}$); δ_C (50 MHz; $CDCl_3$) 165.7 ($C_{2\ oxaz.}$), 156.9 ($C_{3\ isoxaz.}$), 131.5, 130.1, 128.6, 128.2, 126.8 (PhCH), 129.2, 127.2 (PhC), 82.9 ($C_{5\ isoxaz.}$), 70.7 ($C_{5\ oxaz.}$), 69.7 ($C_{4\ oxaz.}$), 38.8 ($C_{4\ isoxaz.}$); m/z (FAB ms) 293 [$(M+H)^+$].

(RR/SS)-3-*phenyl*-5-(2-*phenyl*-4,5-*dihydro-oxazol*-4-*yl*)-2-*isoxazoline* **(26b)** was isolated as a white solid (23 mg, 27 %), m.p. 117-120°C (Found: $(M+H)^+$, 293.12898. $C_{18}H_{17}N_2O_2$ requires $(M+H)$, 293.12899); δ_H (360 MHz; $CDCl_3$) 7.92-7.89 (2H, m, ArH), 7.66-7.63 (2H, m, ArH), 7.40-7.34 (6H, m, ArH), 5.07 (1H, ddd, J_{H5H4a} 10.9 Hz, J_{H5H4b} 8.2 Hz, $J_{H5H4'}$ 3.8 Hz, $H_{5\ isoxaz.}$), 4.71 (1H, ddd, $J_{H4'H5a'}$ 9.8 Hz, $J_{H4'H5b'}$ 7.2 Hz, $J_{H4'H5}$ 3.8 Hz, $H_{4'\ oxaz.}$), 4.48 (1H, dd, $J_{H5a'H4'}$ 9.8 Hz, $J_{H5a'H5b'}$ 9.0 Hz, $H_{5a'\ oxaz.}$), 4.41 (1H, dd, $J_{H5b'H5a'}$ 9.0 Hz, $J_{H5b'H4'}$ 7.2 Hz, $H_{5b\ oxaz.}$), 3.39 (1H, dd, J_{H4aH4b} 16.9 Hz, J_{H4aH5} 10.9 Hz, $H_{4a\ isoxaz.}$), 3.30 (1H, dd, J_{H4bH4a} 16.9 Hz, J_{H4bH5} 8.2 Hz, $H_{4b\ isoxaz.}$); δ_C (50 MHz; $CDCl_3$) 165.6 ($C_{2\ oxaz.}$), 156.5 ($C_{3\ isoxaz.}$), 131.4, 129.9, 128.5, 128.3, 126.6 (PhCH), 129.2, 127.2 (PhC), 81.2 ($C_{5\ isoxaz.}$), 68.6 ($C_{4\ oxaz.}$), 68.5 ($C_{5\ oxaz.}$), 36.2 ($C_{4\ isoxaz.}$); m/z (FAB ms) 293 [$(M+H)^+$].

HPLC analysis of the reaction mixture (reverse phase column, eluted with H_2O/MeOH, 2:3) gave an isomer ratio (26a:26b) of 76:24.

3.5.3. With bromonitrile oxide.

To a stirred solution of alkene **(11)** (0.197 g, 1.14 mmol) and

dibromoformaldoxime (0.252 g, 1.25 mmol) in ether (10 ml), at room temperature, was added a solution of triethylamine (0.14 g, 1.37 mmol) in ether (10 ml) over 15 hours. On completion of the addition, stirring was continued for 1 hour before adding water (30 ml) and separating the organic layer. The aqueous phase was extracted with ether (2 x 30 ml), and the combined organic extract dried over $MgSO_4$ and concentrated *in vacuo*. 90% of the crude reaction product was subjected to flash column chromatography (EtOAc/hexane, 3:17) (10% was set aside for HPLC analysis). Two products were isolated, both of which required further purification. (RS/SR)-3-*bromo*-5-(2-*phenyl*-4,5-*dihydro-oxazol*-4-*yl*)-2-*isoxazoline* **(37a)** (68 mg, 20%) (after dry flash chromatography, hexane then EtOAc/hexane, 3:17) m.p. 79-81°C (Found: $(M+H)^+$, 295.00827. $C_{12}H_{12}BrN_2O_2$ requires $(M+H)$, 295.00826); δ_H (200 MHz; C_6D_6) 8.10-8.05 (2H, m, ArH), 7.11-7.04 (3H, m, ArH), 3.97-3.80 (4H, m, $H_{5\ isoxaz.}$, and $H_{4'}$, $H_{5a'}$, $H_{5b'\ oxaz.}$), 2.89 (1H, dd, J_{H4aH4b} 17.4 Hz, J_{H4aH5} 6.3 Hz, $H_{4a\ isoxaz.}$), 2.57 (1H, dd, J_{H4bH4a} 17.4 Hz, J_{H4bH5} 9.9 Hz, $H_{4b\ isoxaz.}$); δ_C (90 MHz; $CDCl_3$) 166.0 ($C_{2'\ oxaz.}$), 139.7 ($C_{3\ isoxaz.}$), 131.7, 128.3 (PhCH), 127.0 (PhC), 83.3 ($C_{5\ isoxaz.}$), 70.4 ($C_{5'\ oxaz.}$), 69.2 ($C_{4'\ oxaz.}$), 45.2 ($C_{4\ isoxaz.}$); m/z (FAB ms) 295 and 297 $[(M+H)^+]$.

(RR/SS)-3-*bromo*-5-(2-*phenyl*-4,5-*dihydro-oxazol*-4-*yl*)-2-*isoxazoline* **(37b)** was isolated as a white solid (after preparative tlc, EtOAc/hexane, 1:1) (30 mg, 9%), m.p. 103.5-104.5°C (Found: $(M+H)^+$, 295.00827. $C_{12}H_{12}BrN_2O_2$ requires $(M+H)$, 295.00826); δ_H (200 MHz; $C_6D_6/CDCl_3$) 7.99-7.94 (2H, m, ArH), 7.16-7.02 (3H, m, ArH), 4.21 (1H, ddd, J_{H5H4b} 11.0 Hz, J_{H5H4a} 7.4 Hz, $J_{H5H4'}$ 2.4 Hz, $H_{5\ isoxaz.}$), 3.99 (1H, t, $J_{H5a'H5b'}$ 5.3 Hz, $J_{H5a'H4'}$ 5.2 Hz, $H_{5a\ oxaz.}$), 3.90 (1H, m, $J_{H4'H5b'}$ 8.7 Hz, $J_{H4'H5a'}$ 5.2 Hz, $J_{H4'H5}$ 2.4 Hz, $H_{4'\ oxaz.}$), 3.80 (1H, dd, $J_{H5b'H4'}$ 8.7 Hz, $J_{H5b'H5a'}$ 5.3 Hz, $H_{5b'\ oxaz.}$), 2.88 (1H, dd, J_{H4aH4b} 17.1 Hz, J_{H4aH5} 7.4 Hz, $H_{4a\ isoxaz.}$), 2.49 (1H, dd,

J_{H4bH4a} 17.1 Hz, J_{H4bH5} 11.0 Hz, $H_{4b\ isoxaz.}$); δ_C (90 MHz; $C_6D_6/CDCl_3$) 166.0 ($C_{2'\ oxaz.}$), 137.3 ($C_{3\ isoxaz.}$), 131.6, 128.4 (PhCH), 127.1 (PhC), 81.7 ($C_{5\ isoxaz.}$), 68.6 ($C_{5'\ oxaz.}$), 68.3 ($C_{4'\ oxaz.}$), 43.1 ($C_{4\ isoxaz.}$); m/z (FAB ms) 295 and 297 [(*M*+H)$^+$].

HPLC analysis of the reaction mixture (reverse phase column, eluted with H_2O/MeOH, 1:1) gave an isomer ratio (37a:37b) of 69:31.

3.6. Preparation of Nitrile Oxide Precursors (40) and (42).

3.6.1. 4-(R/S)-4-*nitromethyl*-2-*phenyl*-4,5-*dihydro*-*oxazole* (42).

A solution containing 4-(*R/S*)-4-iodomethyl-2-phenyl-4,5-dihydro-oxazole **(34)** (0.5 g, 1.74 mmol), phloroglucinol (0.56 g, 3.48 mmol) and sodium nitrite (0.27 g, 4.0 mmol) in dry DMSO (7 ml) was stirred for 4 days at room temperature. The solvent was then evaporated *in vacuo*, and the residue poured into water (10 ml) and extracted with ethyl acetate (4 x 20 ml). The combined organic extract was dried over $MgSO_4$ and the solvent evaporated under reduced pressure. Flash column chromatography (EtOAc/light petrol, 1:1) furnished a white solid which was recrystallised from hexane to give fine white needles (0.23 g, 63%), m.p. 82-82.5°C (Found: C, 57.9; H, 4.79; N, 13.4. $C_{10}H_{10}N_2O_3$ requires C, 58.2; H, 4.89; N, 13.59%); $\nu_{max.}$ (Nujol) 1640 (C=N), 1545 and 1375 cm^{-1} (NO_2); δ_H (200 MHz; $CDCl_3$), 7.94-7.90 (2H, m, ArH), 7.55-7.36 (3H, m, ArH), 4.94 (1H, dddd, J_{H4H5a} 9.4 Hz, $J_{H4CH2\text{-}4\alpha}$ 8.6 Hz, J_{H4H5b} 7.1 Hz, $J_{H4CH2\text{-}4\alpha}$ 4.7 Hz, H_4), 4.76 (1H, dd, $J_{CH2\text{-}4\alpha(gem)}$ 13.5 Hz, $J_{CH2\text{-}4\alpha H4}$ 4.7 Hz, $O_2NCH\mathit{H}$), 4.64 (1H, t, J_{H5aH5b} 9.3 Hz, J_{H5aH4} 9.4 Hz, H_{5a}), 4.42 (1H, dd, $J_{CH2\text{-}4\alpha(gem)}$ 13.3 Hz, $J_{CH2\text{-}4\alpha H4}$ 8.6 Hz, $O_2NC\mathit{H}H$), 4.36 (1H, dd, J_{H5bH5a} 9.2 Hz, J_{H5bH4} 7.1 Hz, H_{5b}); δ_C (50 MHz; $CDCl_3$) 166.1 (C_2), 131.9, 128.3 (Ph), 77.5 (O_2NCH_2), 70.7 (C_5), 63.9 (C_4), m/z (FAB ms) 207 [(*M*+H)$^+$].

3.6.2. (4R)-4-*aldoximino*-3-(N-t-*butoxycarbonyl*)-2,2-*dimethyloxazolidine* **(40).**

To a stirred solution of hydroxylamine hydrochloride (0.237 g, 3.92 mmol) in pyridine (10 ml) was added a solution of the impure aldehyde **(18)** (0.5 g, 2.18 mmol) in pyridine (5 ml). After stirring for 2 hours no aldehyde remained (tlc, EtOAc/hexane, 5% phosphomolybdic acid/EtOH). The reaction mixture was concentrated *in vacuo*, poured into water and extracted with ethyl acetate (3 x 40 ml). The combined organic extract was dried over $MgSO_4$ and the solvent evaporated under reduced pressure affording a clear viscous oil. Flash column chromatography (EtOAc/hexane, 3:17) furnished a clear oil (0.21 g, 40%) as a (2:3) mixture of *cis* and *trans* isomers (Found: C, 54.33; H, 8.45; N, 11.58. $C_{11}H_{20}N_2O_4$ requires C, 54.1; H, 8.2; N, 11.5%); $\nu_{max.}$ (neat) 3390 (br) (O-H), 1690 cm^{-1} (C=O); δ_H (200 MHz, C_6D_6, 60°C) 8.1 (1H, br.s, OH), 7.33 (0.6H, d, $J_{H\text{-}4\alpha H4}$ 6.0 Hz, HON=C*H*), 6.68 (0.4H, d, $J_{H\text{-}4\alpha H4}$ 5.4 Hz, HON=C*H*), 4.99-4.93 (0.4H, m, H_4), 4.36-4.31 (0.6H, m, H_4), 3.98 (0.6H, dd, J_{H5aH5b} 9.1 Hz, J_{H5aH4} 6.9 Hz, H_{5a}), 3.82-3.74 (1.5H, m, H_{5a}, H_{5b}, H_{5b}), 1.53, 1.52, 1.43 (6H, 3s, OC(CH_3)$_2$N), 1.36, 1.35 (9H, 2s, *t*-Bu); δ_C (50 MHz, C_6D_6, 60°C) 153.4, 149.9 (C=O, C=N), 94.5, 94.4 (C_2), 80.5 (O*C*Me$_3$), 67.0, 66.4 (C_5), 56.6, 53.5 (C_4), 28.5 (OC*Me*$_3$), 26.7, 24.5 (OC(*C*H$_3$)$_2$N); m/z (FAB ms) 245 [(*M*+H)$^+$].

3.7. Cycloaddition Reactions of 4-(*R/S*)-2-phenyl-4,5-dihydro-oxazole-4-carbonitrile oxide and (4*R*)-3-(*N*-*t*-butoxycarbonyl)-2,2-dimethyloxazolidine-4-carbonitrile oxide.

3.7.1. Cycloaddition Reactions of 4-(*R/S*)-2-phenyl-4,5-dihydro-oxazole-4-carbonitrile oxide.

The title nitrile oxide was generated from 4-(*R/S*)-4-nitromethyl-2-phenyl-

4,5-dihydro-oxazole **(42)** by the procedure of Mukaiyama.[45]

3.7.1.1. With styrene (procedure A).

A solution of 4-(*R/S*)-4-nitromethyl-2-phenyl-4,5-dihydro-oxazole **(42)** (0.15 g, 0.73 mmol), *p*-chlorophenyl isocyanate (0.485 g, 3.16 mmol), styrene (0.152 g, 1.46 mmol) and triethylamine (2 drops) in toluene was stirred at room temperature for 18 hours. Ether (5 ml) and diaminoethane (0.15 g, 2.44 mmol) was then added, and stirring continued for 30 minutes, before filtering of the precipitate and washing with several portions of ethyl acetate. The combined filtrate and washings was concentrated *in vacuo* furnishing a yellow solid, 66% of which was subjected to preparative tlc (EtOAc/hexane, 1:19, eluted twice) which gave two products. (RS/SR)-4,5-*di*-(2-*phenyl*-4,5-*dihydro-oxazol*-4-*yl*)*furazan*-N-*oxide* **(45a)** was isolated as a crystalline solid (25 mg, 27%), m.p. 149-150°C (Found: $(M+H)^+$ 377.12496. $C_{20}H_{17}N_4O_4$ requires $(M+H)$, 377.12497); δ_H (200 MHz; $CDCl_3$) 8.03-7.97 (2H, m, ArH), 7.92-7.86 (2H, m, ArH), 7.55-7.33 (6H, m, ArH), 5.57 (1H, dd, J_{H4H5a} 7.9 Hz, J_{H4H5b} 10.2 Hz, H_4), 5.48 (1H, dd, $J_{H4'H5a'}$ 10.2 Hz, $J_{H4'H5b'}$ 9.0 Hz, $H_{4'}$), 5.02 (1H, dd, J_{H5aH4} 7.9 Hz, J_{H5aH5b} 8.9 Hz, H_{5a}), 4.80 (1H, dd, $J_{H5a'H4'}$ 10.2 Hz, $J_{H5a'H5b'}$ 8.6 Hz, $H_{5a'}$), 4.74 1H, t, $J_{H5b'H4'}$ 9.0 Hz, $J_{H5b'H5a'}$ 8.6 Hz, $H_{5b'}$), 4.66 (1H, dd, J_{H5bH4} 10.2 Hz, J_{H5bH5a} 8.9 Hz, H_{5b}); m/z (FAB ms), 377 $[(M+H)^+]$. (RR/SS)-4,5-*di*-(2-*phenyl*-4,5-*dihydro-oxazol*-4-*yl*)*furazan*-N-*oxide* **(45b)** was isolated as a crystalline solid (19 mg, 21%), m.p. 144-145°C (Found: $(M+H)^+$,377.12496. $C_{20}H_{17}N_4O_4$ requires $(M+H)$, 377.12497); δ_H (200 MHz; $CDCl_3$) 7.93-7.71 (4H, m, ArH), 7.52-7.24 (6H, m, ArH), 5.71 (1H, dd, *J* 9.2, 10.5 Hz, H_4), 5.65 (1H, dd, *J* 10.5, 8.9 Hz, $H_{4'}$), 4.91 (1H, t, *J* 8.8, H_{5a}), 4.81-4.62 (3H, m, H_{5b}, $H_{5a'}$, $H_{5b'}$); m/z (FAB ms) 377 $[(M+H)^+]$.

3.7.1.2. With styrene (Procedure B).

To a stirred solution of tolylene 2,4-di-isocyanate (0.174 g, 1.0 mmol), styrene (0.091 g, 0.8 mmol), and triethylamine (0.02 g, 0.2 mmol) in 1,2-dichloroethane (10 ml) was added, over 4 hours, a solution of 4-(*R/S*)-4-nitromethyl-2-phenyl-4,5-dihydro-oxazole **(42)** (0.092 g, 0.4 mmol) in 1,2-dichloroethane (6 ml). When the addition was complete the reaction mixture was refluxed for 1 hour, then cooled to room temperature, treated with 1,2-diaminoethane (0.072 g, 1.2 mmol) and stirred for a further 30 minutes. After filtration through Celite, tlc of the crude product (EtOAc/hexane, 3:7) showed incomplete consumption of the starting material.

The crude product in 1,2-dichloroethane (5 ml) was added dropwise over 3 hours to a solution of styrene (0.092 g, 0.4 mmol), tolylene 2,4-di-isocyanate (0.174 g, 1.0 mmol) and triethylamine (0.02 g, 0.2 mmol) in 1,2-dichloroethane (10 ml). When the additions was complete the reaction mixture was treated as before. The crude product, after filtration and concentration *in vacuo,* was subjected to preparative tlc (EtOAc/hexane, 3:7, eluted twice) which furnished two products.

(RS/S R)-5-*phenyl*-3-(2-*phenyl*-4,5-*dihydro*-*oxazol*-4-*yl*)-2-*isoxazoline* **(46a)** was isolated as a white crystalline solid (42 mg, 32%), m.p. 135-136°C (Found: $(M+H)^+$, 293.12898. $C_{18}H_{17}N_2O_2$ requires $(M+H)$, 293.12899); δ_H (200 MHz, $CDCl_3$) 8.0-7.9 (2H, m, ArH), 7.55-7.30 (8H, m, ArH), 5.65 (1H, dd, J_{H5H4a} 11.0 Hz, J_{H5H4b} 8.8 Hz, $H_{5\ isoxaz.}$), 5.20 (1H, dd, $J_{H4'H5a'}$ 7.6 Hz, $J_{H4'H5b'}$ 10.1 Hz, $H_{4'\ oxaz.}$), 4.73 (1H, dd, $J_{H5a'H5b'}$ 8.8 Hz, $J_{H5a'H4'}$ 7.6 Hz, $H_{5a'\ oxaz.}$), 4.63 (1H, dd, $J_{H5b'H5a'}$ 8.8 Hz, $J_{H5b'H4'}$ 10.1 Hz, $H_{5b'\ oxaz.}$), 3.59 (1H, ddd, J_{H4aH4b} 17.3 Hz, J_{H4aH5} 11.0 Hz, $J_{H4aH4'}$ 0.8 Hz, $H_{4a\ isoxaz.}$), 3.05 (1H, ddd, J_{H4bH4a} 17.3 Hz, J_{H4bH5} 8.8 Hz, $J_{H4bH4'}$ 0.95 Hz, $H_{4b\ isoxaz.}$); m/z (FAB ms) 293 $[(M+H)^+]$.

(RR/SS)-5-*phenyl*-3-(2-*phenyl*-4,5-*dihydro-oxazol*-4-*yl*)-2-*isoxazoline* **(46b)** was isolated as a clear oil (35 mg, 27%), (Found: $(M+H)^+$, 293.12898. $C_{18}H_{17}N_2O_2$ requires $(M+H)$, 293.12899); δ_H (200 MHz, $CDCl_3$), 7.96-7.91 (2H, m, ArH), 7.54-7.35 (3H, m, ArH), 7.3-7.27 (5H, m, ArH), 5.64 (1H, dd, J_{H5H4a} 11.0 Hz, J_{H5H4b} 8.6 Hz, $H_{4\ isoxaz.}$), 5.25 (1H, dd, $J_{H4'H5a'}$ 8.4 Hz, $J_{H4'H5b'}$ 9.4 Hz, $H_{4'\ oxaz.}$), 4.7-4.5 (2H, m, $H_{5a'}$ & $H_{5b'\ oxaz.}$), 3.48 (1H, ddd, J_{H4aH4b} 17.3 Hz, J_{H4aH5} 10.9 Hz, $J_{H4aH4'}$ 0.8 Hz, $H_{4a\ isoxaz.}$), 3.10 (1H, ddd, J_{H4bH4a} 17.3 Hz, J_{H4bH5} 8.7 Hz, $J_{H4bH4'}$ 0.8 Hz, $H_{4b\ isoxaz.}$); m/z (FAB ms) 293 $[(M+H)^+]$.

3.7.1.3. With oct-1-ene.

To a stirred solution of oct-1-ene (0.116 g, 1.04 mmol), triethylamine (0.027 g, 0.26 mmol) and tolylene 2,4-di-isocyanate (0.226 g, 1.3 mmol) in dry 1,2-dichloroethane (7 ml), under reflux, was added a solution of 4-(*R/S*)-4-nitromethyl-2-phenyl-4,5-dihydro-oxazole **(42)** (0.107 g, 0.52 mmol) in 1,2-dichloroethane over 4 hours. When the addition was complete refluxing was continued for a further 2 hours; the reaction mixture was then cooled to room temperature and treated with 1,2-diaminoethane (0.156 g, 1.7 mmol) in ether (3 ml). After 20 minutes the reaction mixture was filtered through Celite and washed with several portions of chloroform. The residue, after evaporation of the solvent, was subjected to flash column chromatography (hexane then EtOAc/hexane, 3:17) (two columns were required to achieve complete separation) which afforded two products.

(RR/SS)-5-*octyl*-3-(2-*phenyl*-4,5-*dihydro-oxazol*-4-*yl*)-2-*isoxazoline* **(47a)** was isolated as a clear oil (76 mg, 49%)[1] which required further purification (preparative tlc, EtOAc/hexane 1:4) (Found: $(M+H)^+$, 301.19160. $C_{18}H_{25}N_2O_2$ requires $(M+H)$, 301.19159); δ_H (200 MHz;

$CDCl_3$) 8.0-7.9 (2H, m, ArH), 7.55-7.37 (3H, m, ArH), 5.16 (1H, dd, $J_{H4'H5a'}$ 8.0 Hz, $J_{H4'H5b'}$ 9.7 Hz, $H_{4'\ oxaz.}$), 4.7-4.5 (3H, m, $H_{5\ isoxaz.}$, $H_{5a'}$ & $H_{5b'\ oxaz.}$), 3.17 (1H, ddd, J_{H4aH4b} 17.2 Hz, J_{H4aH5} 10.5 Hz, $J_{H4aH4'}$ 0.7 Hz, $H_{4a\ isoxaz.}$), 2.66 (1H, ddd, J_{H4bH4a} 17.2 Hz, J_{H4bH5} 8.6 Hz, $J_{H4bH4'}$ 0.8 Hz, $H_{4b\ isoxaz.}$), 1.78-1.13 (10H, m, $5xCH_2$), 0.87 (3H, t, CH_3); m/z (FAB ms) 301 [(*M*+H)$^+$].

(RS/SR)-5-*octyl*-3-(2-*phenyl*-4,5-*dihydro-oxazol*-4-*yl*)-2-*isoxazoline* (**47b**) was isolated as a white powder (44 mg, 28%), m.p. 83-84°C (from methanol) (Found: (*M*+H)$^+$, 301.19160. $C_{18}H_{25}N_2O_2$ requires (*M*+H), 301.19159); δ_H (200 MHz; $CDCl_3$) 7.97-7.93 (2H, m, ArH), 7.53-7.37 (3H, m, ArH), 5.16 (1H, t, $J_{H4'H5a'}$ 9.3 Hz, $J_{H4'H5b'}$ 8.5 Hz, $H_{4'\ oxaz.}$), 4.66-4.54 (1H, m, $H_{5\ isoxaz.}$), 4.61 (1H, d, $J_{H5b'H4'}$ 8.4 Hz, $H_{5b'\ oxaz.}$), 4.60 (1H, d, $J_{H5a'H4'}$ 9.3 Hz, $H_{5a'\ oxaz.}$), 3.08 (1H, dd, J_{H4aH4b} 17.1 Hz, J_{H4aH5} 10.3 Hz, $H_{4a\ isoxaz.}$), 2.73 (1H, dd, J_{H4bH4a} 17.1 Hz, J_{H4bH5} 8.5 Hz, $H_{4b\ isoxaz.}$), 1.68-1.25 (10H, m, $5xCH_2$), 0.86 (3H, t, CH_3); δ_C (90 MHz; $CDCl_3$) 165.6 ($C_{2'\ oxaz.}$), 158.2 ($C_{3\ isoxaz.}$), 131.7, 128.34, 128.29 (PhCH), 127.1 (PhC), 81.1 ($C_{5\ isoxaz.}$), 69.7 ($C_{5\ oxaz.}$), 64.0 ($C_{4\ oxaz.}$), 39.5 ($C_{4\ isoxaz.}$), 35.0, 31.6, 28.9, 25.3, 22.4 ($5XCH_2$), 13.9 (CH_3); m/z (FAB ms) 301 [(*M*+H)$^+$].

1) Not pure.

3.7.2. Cycloaddition Reactions of (4*R*)-3-(*N*-*t*-butoxycarbonyl)-2,2-dimethyloxzolidine-4-carbonitrile oxide (**39**).

The title nitrile oxide was generated *in situ* by the NCS procedure developed by Torssell.[40]

3.7.2.1. With styrene.

To a stirred solution of oxime (**40**) (0.5 g, 1.05 mmol) and pyridine (1 drop) in dry chloroform (10 ml), at room temperature, was added, in one portion, NCS (0.27 g, 2.05 mmol). After 1.5 hours styrene (0.426 g, 4.1

mmol) was added, followed by dropwise addition of a solution of triethylamine (0.21 g, 2.08 mmol) in dry chloroform (10 ml) over 6 hours. After stirring for a further 1 hour after completion of the addition the reaction mixture was poured into water (50 ml). The organic layer was separated and washed with water (2 x 50 ml), brine (50 ml) and dried over $MgSO_4$. Half of the crude product was set aside, the other half was subjected to flash column chromatography (EtOAc/hexane, 1:19) which afforded two products.

(5R,4'R)-5-*phenyl*-3-[3'-(N-t-*butoxycarbonyl*)-2',2'-*dimethyloxazolidin*-4'-*yl*]-2-*isoxazoline* (**49a**) was isolated as a clear oil which solidified on standing (0.137g, 39%), m.p. 71-72°C (from hexane) (Found: $(M+H)^+$ 347.19705. $C_{19}H_{27}N_2O_4$ requires (M+H), 347.19707); $[\alpha]_D$ (20°C) -252.4° (c 0.8 in $CHCl_3$); δ_H (200 MHz; $CDCl_3$, 60°C) 7.32-7.23 (5H, m, ArH); 5.55 (1H, dd, J_{H5H4a} 10.9 Hz, J_{H5H4b} 7.8 Hz, $H_{5\ isoxaz.}$), 4.78 (1H, dd, $J_{H4'H5a'}$ 6.5 Hz, $J_{H4'H5b'}$ 2.6 Hz, $H_{4'\ oxaz.}$), 4.10 (1H, dd, $J_{H5a'H5b'}$ 9.3 Hz, $J_{H5a'H4'}$ 6.5 Hz, $H_{5a'\ oxaz.}$), 3.95 (1H, br.d, $H_{5b'\ oxaz.}$), 3.37 (1H, ddd, J_{H4aH4b} 17.0 Hz, J_{H4aH5} 10.9 Hz, $J_{H4aH4'}$ 0.5 Hz, $H_{4a\ isoxaz.}$), 2.93 (1H, dd, J_{H4bH4a} 17.0 Hz, J_{H4bH5} 7.8 Hz, $H_{4b\ isoxaz.}$), 1.55, 1.49 (6H, 2s, $OC(CH_3)_2N$), 1.45 (9H, s, *t*-Bu); δ_C (50 MHz; $CDCl_3$, 60°C) 157.8 (C=O), 151.6 ($C_{3\ isoxaz.}$), 140.9 (PhC), 128.4, 127.8, 125.4 (PhCH), 94.3 ($C_{2'\ oxaz.}$), 81.8 ($C_{5\ isoxaz.}$), 80.4 ($OCMe_3$), 66.3 ($C_{5'\ oxaz.}$), 54.6 ($C_{4'\ oxaz.}$), 42.6 ($C_{4'\ oxaz.}$), 28.2 ($OCMe_3$), 26.1 (CH_3), 23.7 (CH_3); m/z (FAB ms) 347 [$(M+H)^+$].

(5S,4'R)-5-*phenyl*-3-[3'-(N-t-*butoxycarbonyl*)-2',2'-*dimethyloxazolidin*-4-*yl*]-2-*isoxazoline* (**49b**) was isolated as a white solid (94 mg, 26%), m.p. 88-89°C (from hexane) (Found: $(M+H)^+$, 347.19705. $C_{19}H_{27}N_2O_4$ requires (M+H), 347.19707); $[\alpha]_D$ (20°C) +69.6° (c 1.25 in $CHCl_3$); δ_H (200 MHz, $CDCl_3$, 60°C) 7.33-7.24 (5H, m, ArH), 5.54 (1H, dd, J_{H5H4a} 10.9 Hz, J_{H5H4b}

8.4 Hz, $H_{5\ isoxaz.}$), 4.81 (1H, dd, $J_{H4'H5a'}$ 6.5 Hz, $J_{H4'H5b'}$ 2.5 Hz, $H_{4'\ oxaz.}$), 4.15 (1H, dd, $J_{H5a'H5b'}$ 9.3 Hz, $J_{H5a'H4'}$ 6.5 Hz, $H_{5a'\ oxaz.}$), 4.00 (1H, dd, $J_{H5b'H5a'}$ 9.3 Hz, $J_{H5b'H4'}$ 2.5 Hz, $H_{5b'\ oxaz.}$), 3.39 (1H, ddd, J_{H4aH4b} 17.1 Hz, J_{H4aH5} 10.9 Hz, $J_{H4aH4'}$ 0.75 Hz, $H_{4a\ isoxaz.}$), 2.95 (1H, ddd, J_{H4bH4a} 17.1 Hz, J_{H4bH5} 8.4 Hz, $J_{H4aH4'}$ 0.7 Hz, $H_{4b\ isoxaz.}$), 1.59, 1.51 (6H, 2s, $OC(CH_3)_2N$), 1.40 (9H, s, *t*-Bu); δ_C (50 MHz; $CDCl_3$, 60°C) 158.2 (C=O), 151.6 ($C_{3\ isoxaz.}$), 141.0 (PhC), 128.5, 127.9, 125.6 (PhCH), 94.4 ($C_{2'\ oxaz.}$), 81.9 ($C_{5\ isoxaz.}$), 80.5 ($OCMe_3$), 66.7 ($C_{5'\ oxaz.}$), 54.6 ($C_{4'\ oxaz.}$), 42.7 ($C_{4\ isoxaz.}$), 28.1 ($OCMe_3$), 26.2 (CH_3), 23.6 (CH_3); m/z (FAB ms) 347 [(*M*+H)$^+$].

3.7.2.2. With oct-1-ene.

To a stirred solution of NCS (0.167 g, 1.25 mmol) in dry chloroform (6 ml) was added the oxime **(40)** (0.3 g, 1.23 mmol) and pyridine (1 drop). This was stirred at 40°C for 2 hours, then cooled to room temperature before adding oct-1-ene (0.28 g, 2.46 mmol) followed by slow addition of a solution of triethylamine (0.17 g, 1.72 mmol) in dry chloroform (5 ml) over 9 hours. When the addition was complete stirring was continued for 1 hour, the reaction mixture was then washed with water (3 x 20 ml), brine (20 ml) and dried over $MgSO_4$. Flash column chromatography of the residue (hexane then EtOAc/hexane, 12:88) allowed, after recolumning of overlapping fractions, complete separation of the two diastereomers.

(5S,4'R)-5-*hexyl*-3-[3'-(N-t-*butoxycarbonyl*)-2',2'-*dimethyloxazolidin*-4-*yl*]-2-*isoxazoline* **(50a)** was isolated as a clear oil (0.144 g, 33%) (Found: (*M*+H)$^+$, 355.25966. $C_{19}H_{35}N_2O_4$ requires (*M*+H), 355.25968); $[\alpha]_D$ (20°C) -33.5° (c 0.8 in $CHCl_3$); $\nu_{max.}$ (neat) 1700 cm^{-1} (C=O); δ_H (360 MHz; $CDCl_3$, 60°C) 4.75 (1H, dd, $J_{H4'H5a'}$ 6.6 Hz, $J_{H4'H5b'}$ 2.0 Hz, $H_{4'\ oxaz.}$), 4.56 (1H, m, $H_{5\ isoxaz.}$), 4.12 (1H, dd, $J_{H5a'H5b'}$ 9.2 Hz, $J_{H5a'H4'}$ 6.6 Hz, $H_{5a'\ oxaz.}$), 4.02-3.85 (1H, br.s, $H_{5b'\ oxaz.}$), 2.98 (1H, dd, J_{H4aH4b} 16.8 Hz, J_{H4aH5} 10.3 Hz, H_{4a}

$_{isoxaz.}$), 2.58 (1H, dd, J_{H4bH4a} 16.8 Hz, J_{H4bH5} 7.9 Hz, $H_{4b\ isoxaz.}$), 1.70-1.28 (25H, br.m, 5xCH_2, *t*-Bu, OC(CH_3)$_2$N), 0.87 (3H, t, CH_3); δ_C (90 MHz, $CDCl_3$, 25°C) 158.3 (C=O), 151.8 ($C_{3\ isoxaz.}$), 94.4 ($C_{2'\ oxaz.}$), 80.8 ($C_{5\ isoxaz.}$), 80.5 (O*C*Me$_3$), 66.6 ($C_{5'\ oxaz.}$), 54.8 ($C_{4'\ oxaz.}$), 39.6 ($C_{4\ isoxaz.}$), 35.1, 31.6, 28.9, 25.2, 22.3 (5xCH_2), 28.3 (OC*Me*$_3$), 26.2 (CH_3), 23.7 (CH_3), 13.7 (CH_3); m/z (FAB ms) 355 [(*M*+H)$^+$].

(5R,4'R)-5-*hexyl*-3-[3'-(N-t-*butoxycarbonyl*)-2',2'-*dimethyloxazolidin*-4-*yl*]-2-*isoxazoline* **(50b)** was isolated as a clear oil (0.159 g, 37%) (Found: (*M*+H)$^+$, 355.25968. $C_{19}H_{35}N_2O_4$ requires (*M*+H), 355.25966); $[\alpha]_D$ (20°C), -9.54° (c 0.65 in $CHCl_3$); $\nu_{max.}$ (neat) 1700 (C=O), 1605 cm^{-1} (C=N); δ_H (360 MHz; $CDCl_3$, 60°C) 4.76 (1H, dd, $J_{H4'H5a'}$ 6.6 Hz, $J_{H4'H5b'}$ 2.0 Hz, $H_{4'\ oxaz.}$), 4.6-4.5 (1H, m, $H_{5\ isoxaz.}$), 4.13 (1H, dd, $J_{H5a'H5b'}$ 9.2 Hz, $J_{H5a'H4'}$ 6.6 Hz, $H_{5a'\ oxaz.}$), 4.0-3.85 (1H, br.d, $H_{5b'\ oxaz.}$), 2.99 (1H, ddd, J_{H4aH4b} 16.9 Hz, J_{H4aH5} 10.2 Hz, $J_{H4aH4'}$ 0.3 Hz, $H_{4a\ isoxaz.}$), 2.57 (1H, dd, J_{H4bH4a} 16.8 Hz, J_{H4bH5} 8.4 Hz, $H_{4b\ isoxaz.}$), 1.7-1.3 (25H, m, 5xCH_2, *t*-Bu, OC(CH_3)$_2$N), 0.88 (3H, t, CH_3); δ_C (90 MHz; $CDCl_3$, 25°C) 158.5 (C=O), 151.8 ($C_{3\ isoxaz.}$), 94.4 ($C_{2'\ oxaz.}$), 80.9 ($C_{5\ isoxaz.}$), 80.5 (O*C*Me$_3$), 66.7 ($C_{5'\ oxaz.}$), 54.8 ($C_{4'\ oxaz.}$), 39.5 ($C_{4\ isoxaz.}$), 35.1, 31.6, 28.9, 25.3, 22.4 (5xCH_2), 28.3 (OC*Me*$_3$), 28.2 (CH_3), 26.2 (CH_3), 13.7 (CH_3); m/z (FAB ms) 355 [(*M*+H)$^+$].

3.7.2.3. With diethylfumarate.

To a stirred solution of the oxime **(40)** (0.5 g, 2.05 mmol) and pyridine (1 drop) in dry chloroform (10 ml) was added, in one portion, NCS (0.27 g, 2.05 mmol). After stirring for 2 hours at room temperature diethylfumarate (0.71 g, 4.1 mmol) was added, followed by slow addition of a solution of triethylamine (0.21 g, 2.08 mmol) in dry chloroform (10 ml) over 16 hours. After stirring for a further hour the reaction mixture was washed with water

(3 x 30 ml), dried over $MgSO_4$ and the solvent evaporated *in vacuo*. Flash column chromatography on 75% of the crude reaction product (EtOAc/hexane, 1:9) afforded pure portions of each of the diastereomeric adducts, along with some mixed fractions. The combined yield of **(51a)** and **(51b)** was 0.304 g, 36%.

The first eluted pure isomer, (4S,4'R,5S)-4,5-*diethoxycarbonyl*-3-[3'(N-t-*butoxycarbonyl*)-2',2'-*dimethyloxazolidin*-4-*yl*]-2-*isoxazoline* **(51a)**[1], (35 mg) was isolated as a clear oil (Found: $(M+H)^+$, 415.20801. $C_{19}H_{31}N_2O_8$ requires $(M+H)$, 415.20802); $[\alpha]_D$ (20°C) -166.2° (c 1.0 in $CHCl_3$); $\nu_{max.}$ (neat) 1740 (C=O), 1700 cm^{-1} (C=O); δ_H (200 MHz; $CDCl_3$, 60°C) 5.15 (1H, d, J_{H5H4} 5.5 Hz, $H_{5\ isoxaz.}$), 4.79 (1H, t, $J_{H4'H5'}$ 5.0 Hz, $H_{4'\ oxaz.}$), 4.47 (1H, d, J_{H4H5} 5.5 Hz, $H_{4\ isoxaz.}$), 4.19 (4H, q, J 7.1 Hz, OCH_2CH_3), 4.09 (2H, d, $J_{H5'H4'}$ 5.0 Hz, $H_{5a'}$ & $H_{5b'\ oxaz.}$), 1.55, 1.47 (6H, 2s, $OC(CH_3)_2N$), 1.41 (9H, s, *t*-Bu), 1.25 (6H, t, J 7.1 Hz, OCH_2CH_3); δ_C (50 MHz; $CDCl_3$, 60°C) 168.4 ($C{=}O_{\ ester}$), 167.4 ($C{=}O_{\ ester}$), 155.6 ($C{=}O_{\ Boc}$), 151.6 ($C_{3\ isoxaz.}$), 94.6 ($C_{2'\ oxaz.}$), 81.3 ($C_{5\ isoxaz.}$), 80.7 ($OCMe_3$), 66.6 ($C_{5'\ oxaz.}$), 62.1, 61.9 (OCH_2CH_3), 57.9, 53.9 ($C_{4'\ oxaz.}$, $C_{4\ isoxaz.}$), 28.1 ($OCMe_3$), 25.6 (CH_3), 24.4 (CH_3), 13.8 (OCH_2CH_3); m/z (FAB ms) 415 $[(M+H)^+]$.

The second eluted pure isomer, (4R,4'R,5R)-4,5-*diethoxycarbonyl*-3-[3'-(N-t-*butoxycarbonyl*)-2',2'-*dimethyloxazolidin*-4-*yl*]-2-*isoxazoline* **(51b)**[1], (46 mg) was isolated as a clear oil (Found: $(M+H)^+$, 415.20801. $C_{19}H_{31}N_2O_8$ requires $(M+H)$, 415.20802); $[\alpha]_D$ (20°C) +102.1° (c 0.7 in $CHCl_3$); $\nu_{max.}$ (neat) 1740 (C=O), 1700 cm^{-1} (C=O); δ_H (200 MHz, $CDCl_3$, 56°C) 5.19 (1H, d, J_{H5H4} 6.3 Hz, $H_{5\ isoxaz.}$), 4.86 (1H, br.dd, $J_{H4'H5a'}$ 5.8 Hz, $J_{H4'H5b'}$ 2.7 Hz, $H_{4'\ oxaz.}$), 4.30 (1H, d, J_{H4H5} 6.3 Hz, $H_{4\ isoxaz.}$), 4.29-4.18 (4H, 2q, OCH_2CH_3), 4.10 (1H, dd, $J_{H5a'H5b'}$ 9.3 Hz, $J_{H5a'H4'}$ 6.0 Hz, $H_{5a'\ oxaz.}$), 4.04 (1H, dd, $J_{H5b'H5a'}$ 9.3 Hz, $J_{H5b'H4'}$ 2.8 Hz, $H_{5b'\ oxaz.}$), 1.63, 1.48

(6H, 2s, OC(CH_3)$_2$N), 1.42 (9H, s, *t*-Bu), 1.29 (6H, t, *J* 7.1 Hz, OCH$_2$CH_3); δ_C (50 MHz; $CDCl_3$, 56°C) 168.3 (C=O $_{ester}$), 167.4 (C=O $_{ester}$), 155.0 (C=O $_{Boc}$), 151.7 ($C_{3\ isoxaz.}$), 94.7 ($C_{2'\ oxaz.}$), 82.2 ($C_{5\ isoxaz.}$), 80.7 (O*C*Me$_3$), 66.0 ($C_{5'\ oxaz.}$), 62.3, 62.1 (O*C*H$_2$CH$_3$), 56.8, 54.5 ($C_{4'\ oxaz.}$, $C_{4\ isoxaz.}$), 29.5 (CH_3), 28.1 (OC*Me*$_3$), 25.8 (CH_3), 13.8 (OCH$_2$*C*H$_3$); m/z (FAB ms) 415 [(*M*+H)$^+$].

1) Arbitrary assignment of stereochemistry.

3.8. Deprotection of (50b).

3.8.1. (5R,2'R)-2'-*amino*-2'-(5-*hexyl*-2-*isoxazolin*-3-*yl*)*ethanol* (57).

A solution of the (5*R*,4'*R*)-5-hexyl-3-(3'-*N*-*t*-butoxycarbonyl-2',2'-dimethyl-oxazolidin-4-yl)-2-isoxazoline **(50b)** (0.082 g, 0.23 mmol) in TFA/H_2O (98:2, 1 ml) was stirred, at room temperature, for 30 minutes, the solvent was then evaporated *in vacuo*. The residue was dissolved in dichloromethane (2 ml) and stirred with saturated sodium carbonate solution (4 ml). The organic layer was separated and the aqueous phase extracted with dichloromethane (2 x 10 ml). The combined organic extract was washed with 10% sodium carbonate solution (10 ml), brine (10 ml), dried over $MgSO_4$, and the solvent evaporated *in vacuo*. The resulting off-white solid was subjected to dry flash chromatography (EtOAc/MeOH, 19:1, with 5 drops of conc. ammonia per 50 ml) which furnished a white solid (31 mg, 63%) which turned slowly yellow on standing at room temperature. (Found: (*M*+H)$^+$, 215.175942. $C_{11}H_{23}N_2O_2$ requires (*M*+H), 215.17594); δ_H (200 MHz; $CDCl_3$) 4.7-4.5 (1H, br.m, H_5), 3.9-3.5 (2H, br.s, CH_2OH), 3.2-2.95 (1H, br.m, H_{4a}), 2.75-2.5 (1H, br.m, H_{4b}), 1.75-1.1 (*ca.* 13 H, br.m, 5xCH_2, NH_2, OH), 0.87 (3H, t, CH_3).

3.8.2. (5*R*,4'*R*)-5-hexyl-3-(2-phenyl-4,5-dihydro-oxazol-4-yl)-2-isoxazoline **(47a).**

To a stirred solution of the amino alcohol **(57)** (18 mg, 0.045 mmol) in dry dichloromethane (1 ml) was added a solution of ethyl benzimidate (16 mg, 0.011 mmol) in dichloromethane (1 ml). After stirring at room temperature for 14 hours the solvent was evaporated and the residue subjected to preparative tlc (EtOAc/hexane, 3:17), which furnished the title compound **(47a)** as a clear oil (11 mg, 44%), [a]D (20oC) +24.5° (c 0.1 in CH_2Cl_2); δ_H (200 MHz; $CDCl_3$) 7.97-7.92 (2H, m, ArH), 7.55-7.37 (3H, m, ArH), 5.20 (1H, t, *J* 9.8 and 8.0 Hz, $H_{4'\ oxaz.}$), 4.69-4.51 (3H, m, $H_{5\ isoxaz.}$, H_{5a} & $H_{5b\ oxaz.}$), 3.17 (1H, dd, J_{H4aH4b} 17.1 Hz, J_{H4aH5} 10.4 Hz, $H_{4a\ isoxaz.}$), 2.66 (1H, dd, J_{H4bH4a} 17.1 Hz, J_{H4bH5} 8.6 Hz, $H_{4b\ isoxaz.}$), 1.75-1.25 (10H, m, 5xCH_2), 0.87 (3H, t, CH_3).

3.9. Synthesis of isoxazole- and 2-isoxazoline-3-aldoximes.

3.9.1. 3-ethoxycarbonyl-5-phenylisoxazole (77a).

A solution of phenylacetylene (25.0 g, 236 mmol) and ethyl chloro-oximidoacetate (36.7 g, 236 mmol) in xylene (200 ml) was heated under reflux for 24 hours. After cooling, the xylene was removed by rotary evaporation, and the residual red/brown oil solidified by standing in the fridge overnight. Recrystallisation from ethanol (x2) furnished **(77a)** as a colourless crystalline solid (35.8 g, 70%), m.p. 50-51.5°C (lit.,[147] 52°C); $\nu_{max.}$ (Nujol) 1740 cm^{-1} (C=O); δ_H (200MHz; $CDCl_3$) 7.78-7.74 (2H, m, ArH), 7.48-7.41 (3H, m, ArH), 6.89 (1H, s, H_4), 4.44 (2H, q, *J* 7 Hz, OCH_2CH_3), 1.41 (3H, t, *J* 7 Hz, OCH_2CH_3); δ_C (50 MHz; $CDCl_3$) 171.5, 159.8, 156.8, (C=O, C_3, C_5), 130.6, 128.9, 125.7 (PhCH), 126.4 (PhC), 99.7 (C_4), 62.0 (OCH_2CH_3), 14.0 (OCH_2CH_3); m/z 217 (M^+, 89%), 171 (33), 145 (32), 105 (100), 77 (45).

3.9.2. 3-*ethoxycarbonyl*-5-*octylisoxazole* (77b).

To a stirred solution of ethyl chloro-oximidoacetate (4.87 g, 32 mmol) and dec-1-yne (8.84 g, 64 mmol) in diethyl ether (50 ml) was added, over *ca.* 32 hours at room temperature, a solution of triethylamine (3.64 g, 36 mmol) in ether (40 ml). After the addition was complete the reaction was stirred for 1 hour, filtered through Celite, and the solvent removed *in vacuo*. The residue was flash column chromatographed (EtOAc/hexane, 1:19) affording **(77b)** as a clear oil (6.42 g, 79%). A sample was Kugelrohr distilled (100°C, 0.005 mbar) (Found: M^+ 253.1672. $C_{14}H_{23}NO_3$ requires *M*, 253.16778); $\nu_{max.}$ (neat) 1665 (C=O), 1595 cm^{-1} (C=N); δ_H (80 MHz; $CDCl_3$) 6.31 (1H, s, H_4), 4.34, (2H, q, *J* 7 Hz, OCH_2CH_3), 2.71 (2H, br.t, α-CH_2), 1.73-1.0 (15H, br.m, 6xCH_2, OCH_2CH_3), 0.77 (3H, br.t, CH_3); δ_C (50 MHz, $CDCl_3$) 175.4, 159.9, 156.0 (C=O, C_3, C_5), 101.1 (C_4), 61.6 (OCH_2CH_3), 31.4, 28.8, 28.6, 27.1, 26.3, 22.3 (6xCH2), 13.8 ($CH_3OCH_2CH_3$); m/z 253 (M^+, 21%), 168 (51), 155 (35), 96 (51).

3.9.3. 3-ethoxycarbonyl-5-phenyl-2-isoxazoline (77c).

To a stirred solution of styrene (9.59 g, 92 mmol) and ethyl chloro-oximidoacetate (7.0 g, 46 mmol) in ether (70 ml) at room temperature, was added, over 6 hours, a solution of triethylamine (5.25 g, 52 mmol) in ether (50 ml). After the addition was complete stirring was continued for 1 hour, the reaction mixture was washed with water (2 x 150 ml), dried over $MgSO_4$ and the solvent evaporated *in vacuo*. Excess styrene was removed by high vacuum rotary evaporation, and the residue Kugelrohr distilled (140°C, 0.2 mmHg) affording a clear oil (9.2 g, 91%) $\nu_{max.}$ (neat) 1720 (C=O), 1595 cm^{-1} (C=N); δ_H (80 MHz; $CDCl_3$) 7.30 (5H, s, ArH), 5.70 (1H, dd, J_{H5H4a} 11.3 Hz, J_{H5H4b} 9.2Hz, H_5), 4.27 (2H, q, *J* 7.1 Hz,

OCH_2CH_3), 3.58 (1H, dd, J_{H4aH4b} 17.7 Hz, J_{H4aH5} 11.3 Hz, H_{4a}), 3.09 (1H, dd, J_{H4bH4a} 17.7 Hz, J_{H4bH5} 9.2 Hz, H_{4b}), 1.29 (3H, t, *J* 7.1 Hz, OCH_2CH_3), δ_C (50 MHz; $CDCl_3$) 160.1 (C=O), 150.8 (C_3), 139.2 (PhC), 128.4, 128.2, 125.5 (PhCH), 84.5 (C_5), 61.6 (OCH_2CH_3), 41.0 (C_4), 13.7 (OCH_2CH_3); m/z 219 (M^+, 4%), 128 (19), 115 (23), 104 (100), 77 (35).

3.9.4. 3-*ethoxycarbonyl*-5-*octyl*-2-*isoxazoline* (**77d**).

To a stirred solution of ethyl chloro-oximidoacetate (3.33 g, 21 mmol) and dec-1-ene (11.2 g, 80 mmol) in ether (150 ml) at room temperature, was added, over *ca.* 7 hours, a solution of triethylamine (3.03 g, 30 mmol). After stirring for a further 1 hour the mixture was filtered through Celite and the solvent evaporated under reduced pressure. The residue was flash column chromatographed (hexane then EtOAc/hexane 1:19) which furnished (**77d**) as a clear oil (5.46 g, 100%). Kugelrohr distillation (110°C, 0.015 mmHg) provided an analytical sample (Found: C, 65.83; H, 9.60; N, 5.66. $C_{14}H_{25}NO_3$ requires C, 65.8; H, 9.9; N, 5.5%); (Found: M^+ 255.1842. $C_{14}H_{25}NO_3$ requires *M*, 255.18343.); $\nu_{max.}$ (neat) 1720 (C=O), 1590 cm^{-1} (C=N); δ_H (80 MHz; $CDCl_3$) 4.95-4.47 (1H, m, H_5), 4.26 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 3.19 (1H, dd, J_{H4aH4b} 17.5 Hz, J_{H4aH5} 10.6 Hz, H_{4a}), 2.73 (1H, dd, J_{H4bH4a} 17.5 Hz, J_{H4bH5} 8.9 Hz, H_{4b}), 1.67-1.20 (17H, m, $7xCH_2$, OCH_2CH_3), 0.81 (3H, t, CH_3); δ_C (50 MHz; $CDCl_3$) 160.6 (C=O), 151.1 (C_3), 83.9 (C_5), 61.6 (OCH_2CH_3), 38.1 (C_4), 34.8, 31.5, 29.1, 29.0, 28.9, 24.8, 22.3, (alkyl chain CH_2s), 13.8 (CH_3, OCH_2CH_3); m/z 255 (M^+, 12%), 182 (52), 142 (86), 116 (38), 114 (21).

3.9.5. 4,5-*dibutyl*-3-*ethoxycarbonylisoxazole* (**77e**).

A solution of ethyl chloro-oximidoacetate (1.09 g, 7.25 mmol) and dec-5-

yne (1.0 g, 7.25 mmol) in xylene (20 ml) was heated under reflux for 23 hours. The solvent was removed *in vacuo* and the residue flash column chromatographed (Et_2O/hexane, 3:97) to furnish the title compound **(77e)** as a clear oil (0.56 g, 31%) (Found: M^+ 253.1617. $C_{14}H_{23}NO_3$ requires *M*, 253.16778); $\nu_{max.}$ (neat) 1730 (C=O), 1620 cm^{-1} (C=N); δ_H (80 MHz; $CDCl_3$) 4.32 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 2.72-2.37 (4H, br.m, 2xα-CH_2), 1.68-1.06 (11H, m, 4xCH_2, OCH_2CH_3), 0.92-0.71 (6H, m, 2xCH_3); δ_C (50 MHz, $CDCl_3$) 170.9, 160.5, 154.1 (C=O, C_3, C_5), 115.4 (C_4), 61.2 (OCH_2CH_3), 32.2, 29.4 (2xα-CH_2), 24.7, 22.1, 21.8, 21.5 (CH_2s), 13.7, 13.4, 13.2 (3xCH_3); m/z 253 (M^+, 13%), 224 (36), 196 (22), 180 (71), 138 (100), 124 (24), 96 (23).

3.9.6. 3-hydroxymethyl-5-phenylisoxazole (78).

The title compound was prepared by the procedure reported by Wade and De Micheli. [134]

To a stirred solution of 3-ethoxycarbonyl-5-phenylisoxazole **(77a)** (7.9 g, 36.1 mmol) in ethanol (200 ml), at room temperature, was added sodium borohydride (6.82 g, 180 mmol). After stirring for 5 hours tlc (Et_2O/hexane, 1:1) showed complete consumption of the ester. The reaction mixture was treated with water (200 ml), and after stirring for 30 minutes extracted with dichloromethane (4 x 100 ml). The combined organic extract was dried over $MgSO_4$, and the solvent evaporated *in vacuo*; the resulting white solid was recrystallised from ethyl acetate to yield a white crystalline solid (5.4 g, 86%), m.p. 100-101°C (lit.,[148] 100-102°C); $\nu_{max.}$ (Nujol) 3320 cm^{-1} (O-H); δ_H (80 MHz; $CDCl_3$) 7.68 (2H, m, ArH), 7.39 (3H, m, ArH), 6.55 (1H, s, H_4), 4.76 (2H, s, CH_2OH), 3.23 (1H, br.s, OH); δ_C (50 MHz; $CDCl_3$) 170.1, 164.2 (C_3, C_5), 130.0, 128.8, 125.6 (PhCH), 127.0 (PhC), 98.2 (C_4),

56.5 (CH_2OH); m/z 175 (M^+, 60%), 145 (10), 105 (100), 77 (42).

3.9.7. 3-formyl-5-phenylisoxazole (79a).

3.9.7.1 Oxidation of 3-hydroxymethyl-5-phenylisoxazole (78) with pyridinium chlorochromate (PCC).[111]

A solution of 3-hydroxymethyl-5-phenylisoxazole **(78)** (2.5 g, 14.3 mmol) in dry dichloromethane (10 ml) was added rapidly to a suspension of PCC (6.16 g, 28.6 mmol) in dichloromethane (120 ml). After stirring for 8.5 hours a large amount of the alcohol had not been consumed (tlc, Et_2O/hexane, 1:1) so a second portion of PCC (3.1 g, 14.3 mmol) was added. After 30 hours the alcohol had been completely consumed. The reaction mixture was diluted with anhydrous ether (600 ml) and the solvent decanted off; the black residue was washed with dry ether (3 x 50 ml). The combined extract was filtered through a pad of Florisil and the solvent evaporated *in vacuo*. Dry flash chromatography (Et_2O/ hexane, 1:4) afforded the title compound **(79a)** as a white powder (2.03 g, 82%), m.p. 57-58.5°C (lit.,[149] 61°C); $\nu_{max.}$ (Nujol) 1715 cm^{-1} (C=O); δ_H (80 MHz; $CDCl_3$) 10.56 (1H, s, C*H*O), 7.85-7.71 (2H, m, ArH), 7.55-7.39 (3H, m, ArH), 6.85 (1H, s, H_4); δ_C (50 MHz; $CDCl_3$) 184.7 (CHO), 171.9, 162.4 (C_3, C_5), 130.8, 129.0, 125.8 (PhCH), 126.2 (PhC), 96.2 (C_4); m/z 173 (M^+, 66%), 105 (*M*-68, 100%).

3.9.7.2. Reduction of 3-ethoxycarbonyl-5-phenylisoxazole (77a) with Di-isobutylaluminium Hydride (DIBAL).[134]

To a stirred cooled (-78°C) solution of 3-ethoxycarbonyl-5-phenylisoxazole **(77a)** (34 g, 157 mmol) in dry dichloromethane (500 ml), under a nitrogen atmosphere, was added DIBAL (1M in hexanes, 390 ml, 390 mmol) at such a rate that the temperature did not exceed -65°C

(*ca.* 1 hour). After stirring for a further 50 minutes, methanol (10 ml) was carefully added, followed by water (5 ml) and 10% aqueous HCl (70 ml). The reaction mixture was allowed to settle and as much solvent as possible was decanted off, the remaining sludge was filtered through Celite and the aluminium salt washed through with several portions of dichloromethane. The combined organic portions were dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The residue was subjected to flash column chromatography (Et_2O/hexane, 1:9 then EtOAc) yielding 3-formyl-5-phenylisoxazole (**79a**) as a white powder (23.05 g, 85%), m.p. 54.5-55.5°C (lit.,[149] 61°C) and 3-hydroxymethyl-5-phenylisoxazole (**78**) (3.45 g, 12%), m.p. 100-102°C (lit.,[148] 100-102°C).

3.9.8. 3-*formyl*-5-*octylisoxazole* (**79b**).

To a stirred cooled (-78°C) solution of 3-ethoxycarbonyl-5-octylisoxazole (**77b**) (6.2 g, 24.4 mmol) in dry dichloromethane (100 ml) under a nitrogen atmosphere, was added DIBAL (1 M. in hexanes, 48.8 ml, 48.8 mmol) at such a rate that the internal temperature did not exceed -65°C. When the addition was complete the reaction was stirred for a further 50 minutes, then quenched with methanol (5 ml) and allowed to warm to room temperature. Aqueous HCl (200 ml, 5%) was added and the organic layer separated; the aqeous portion was extracted with dichloromethane (2 x 100 ml). The combined organic extract was dried over $MgSO_4$, and the solvent evaporated *in vacuo* furnishing a yellow oil (4.96 g); Kugelrohr distillation (70°C, 0.01 mbar) yielded a clear oil (4.39 g, 87%), (Found: M^+, 209.1414. $C_{12}H_{19}NO_2$ requires *M*, 209.14157); $\nu_{max.}$ (neat) 1715 (C=O), 1595 cm^{-1} (C=N); δ_H (80 MHz; $CDCl_3$), 9.95 (1H, s, C*H*O), 6.29 (1H, s, H_4), 2.71 (2H, br.t, α-CH_2), 1.69-1.16 (12H, m, 6xCH_2), 0.76 (3H, t, CH_3); δ_C (50 MHz; $CDCl_3$) 184.7 (C=O), 175.8, 161.9 (C_3, C_5), 97.6 (C_4), 31.5. 29.5,

28.8, 27.1, 26.4, 22.3 (6xCH_2), 13.8 (CH_3); m/z 209 (*M*+, 8%), 180 (23), 124 (26), 111 (23), 83 (43), 68 (100).

3.9.9. 3-formyl-5-phenyl-2-isoxazoline (**79c**)[134]

To a stirred cooled (-78°C) solution of 3-ethoxycarbonyl-5-phenyl-2-isoxazoline (**77c**) (8.23 g, 37.5 mmol) in dry dichloromethane (120 ml) under a nitrogen atmosphere, was added DIBAL (1M in hexanes, 75 ml, 75 mmol) at such a rate that the internal temperature did not exceed -65°C. After stirring for a further 50 minutes, methanol (6 ml) was added and the reaction allowed to warm to room temperature. Aqueous HCl (100 ml, 5%) was added and the organic layer separated; the aqueous portion was extracted with dichloromethane (2 x 100 ml), and the combined organic extract dried over $MgSO_4$. Evaporation of the solvent *in vacuo* furnished a brown oil which was subjected to flash column chromatography (EtOAc/hexane, 1:19)[1] yielding a clear oil (3.36 g, 51%), $\nu_{max.}$ (neat) 1690 (C=O), 1585 cm^{-1}(C=N); δ_H (80 MHz, $CDCl_3$) 9.91 (1H, s, C*H*O), 7.42-7.19 (5H, m, ArH), 5.76 (1H, dd, J_{H5H4a} 11.3 Hz, J_{H5H4b} 9.1 Hz, H_5), 3.50 (1H, dd, J_{H4aH4b} 17.6 Hz, J_{H4aH5} 11.3 Hz, H_{4a}), 3.03 (1H, dd, J_{H4bH4a} 17.6 Hz, J_{H4bH5} 9.1 Hz, H_{4b}); δ_C (50 MHz, $CDCl_3$) 185.2, 185.1 (CHO), 158.6 (C_3), 138.8 (PhC), 128.6, 128.5, 125.6 (PhCH), 85.6 (C_5), 37.7 (C_4); m/z 175 (*M*+, 20%), 117 (36), 104 (100), 77 (30).

1. Attempted Kugelrohr distillation of the crude aldehyde led to some decomposition.

3.9.10. 3-*formyl*-5-*octyl*-2-*isoxazoline* (**79d**).

To a stirred cooled (-78°C) solution of 3-ethoxycarbonyl-5-octyl-2-isoxazoline (**77d**) (6.0 g, 23.5 mmol) in dry dichloromethane (100 ml) under an atmosphere of nitrogen, was added DIBAL (1M in hexanes, 47 ml, 47 mmol) over 10 minutes. After stirring for 1 hour the reaction was

quenched with methanol (5 ml) and allowed to warm to room temperature; aqueous HCl (200 ml, 5%) was added and the organic layer separated, the aqueous portion was extracted with dichloromethane (2 x 100 ml). The combined organic extract was washed with water (200 ml), dried over $MgSO_4$ and the solvent evaporated *in vacuo* to give an orange/brown oil. Kugelrohr distillation (100°C, 0.05 mmHg) furnished the title compound **(79d)** as a clear oil (3.61 g, 73%), (Found: *M*+, 211.1566. $C_{12}H_{21}NO_2$ requires *M*, 211.15722); $\nu_{max.}$ (neat) 1695 (C=O), 1585 cm^{-1} (C=N); δ_H (80 MHz; $CDCl_3$) 9.81 (1H, s, C*H*O), 4.81-4.56 (1H, m, H_5), 3.08 (1H, dd, J_{H4aH4b} 17.3 Hz, J_{H4aH5} 10.7 Hz, H_{4a}), 2.62 (1H, dd, J_{H4bH4a} 17.3 Hz, J_{H4bH5} 8.8 Hz, H_{4b}), 1.68-0.98 (14H, br.m, 7xCH_2), 0.8 (3H, t, CH_3); δ_C (50 MHz, $CDCl_3$) 185.7, 185.6 (C=O), 159.1 (C_3), 85.1 (C_5), 34.8 (C_4), 31.5, 29.0, 24.8, 22.4 (alkyl CH_2s), 13.8 (CH_3); m/z 211 (*M*+, 4%), 182 (21), 141 (19), 123 (12).

3.9.11. 4,5-*dibutyl*-3-*formylisoxazole* **(79e).**

To a stirred solution of 4,5-dibutyl-3-ethoxycarbonylisoxazole **(77e)** (0.5 g, 1.98 mmol) in dichloromethane (20 ml), cooled to -78°C and under a nitrogen atmosphere, was added DIBAL (1M in hexanes, 7.9 ml, 7.9 mmol). After stirring for 1 hour the reaction was quenched with methanol (2 ml) and then allowed to warm to room temperature and poured into aqueous HCl (40 ml, 5%). The organic layer was separated and the aqueous portion extracted with dichloromethane (2 x 40 ml); the combined extract was dried over $MgSO_4$ and the solvent evaporated *in vacuo* yielding a straw-coloured oil. Flash column chromatography (Et_2O/light petrol, 1:4) furnished a clear oil (0.35 g, 83%), (Found: *M*+, 209.1419. $C_{12}H_{19}NO_2$ requires *M*, 209.14157); $\nu_{max.}$ (neat) 1710 (C=O),

1620 cm^{-1} (C=N); δ_H (80 MHz; $CDCl_3$) 10.12 (1H, s, C*H*O), 2.79-2.43 (4H, br.m, 2xα-CH_2s), 1.75-1.13 (8H, m, 4xCH_2), 0.99-0.78 (6H, m, 2xCH_3); δ_C (50 MHz; $CDCl_3$) 186.4 (CHO), 171.6, 159.7 (C_3, C_5), 114.1 (C_4), 32.1, 29.6, 24.7, 22.2, 22.1, 21.3 (6xCH_2), 13.6, 13.5 (2xCH_3); m/z 209 (*M*+,14%), 138 (16), 124 (14), 85 (31).

3.9.12. 3-aldoximino-5-phenylisoxazole **(80a)**.

3.9.12.1. Preparation with Pyridine as the Solvent.

To a stirred solution of hydroxylamine hydrochloride (4.21 g, 60.6 mmol) in pyridine (70 ml), at room temperature, was added a solution of 3-formyl-5-phenylisoxazole **(79a)** (7.0 g, 40.4 mmol). Stirring was continued for 2 hours, the reaction mixture was then concentrated *in vacuo*, and the residue poured into water and extracted with ethyl acetate (3 x 100 ml). The combined organic extract was washed with water (2 x 50 ml), 10% aqueous HCl solution (3 x 50 ml), dried over $MgSO_4$ and the solvent evaporated *in vacuo* to give a white solid. Recrystallisation from toluene furnished fine white platelets (6.88 g, 90%), m.p. 140-144°C, (lit.,[149] 145°C); $\nu_{max.}$ (Nujol) 3220 cm^{-1} (O-H); δ_H (80 MHz; $(CD_3)_2CO$) 11.20 (1H, br.s, OH), 8.25 (1H, d, $J_{H3\alpha H4}$ 0.4 Hz, HON=C*H*), 7.95-7.77 (2H, m, ArH), 7.58-7.42 (3H, m, ArH), 7.02 (1H, d, $J_{H4H3\alpha}$ 0.4 Hz H_4), δ_C (50 MHz; $(CD_3)_2CO$) 168.5, 158.2 (C_3, C_5), 138.7,138.6 (HON=*C*H), 129.4, 128.0, 126.0, 124.7, (Ph), 95.6, 95.5 (C_4); m/z 188 (*M*+, 91%) 105 (100), 77 (82).

3.9.12.2. Preparation Using a Two Phase System

To an aqueous solution of sodium hydroxide (0.3 g, 7.5 mmol, 1.0 ml H_2O) was added hydroxylamine hydrochloride (0.52 g, 7.5 mmol), followed by

a solution of 3-formyl-5-phenylisoxazole **(79a)** (1.0 g, 5.78 mmol) in chloroform (10 ml). A thick white precipitate formed immediately. The solvent was removed *in vacuo* and the solid suspended in ethyl acetate (50 ml) and shaken with 1 molar aqueous potassium hydrogen sulphate solution (this brought about the dissolution of the precipitate). The organic layer was separated and the aqueous portion extracted with ethyl acetate (2 x 50 ml); the combined organic extract was dried over $MgSO_4$ and the solvent evaporated under reduced pressure. Analysis of the product by tlc (EtOAc/hexane, 1:1) showed it to be a mixture of aldehyde and oxime.

The mixture was resubjected to the reaction conditions (NaOH, 0.34 g, 8.4 mmol; $NH_2OH.HCl$, 0.58 g, 8.3 mmol); after stirring for several hours a further equivalent of sodium hydroxide and hydroxylamine was added and the reaction stirred overnight. The work-up was carried out as previously described yielding an off-white powder. Recrystallisation from toluene furnished the oxime **(80a)** (0.76 g, 70%), m.p. 141-144°C (lit.,[149] 145°C).

3.9.13. 3-*aldoximino*-5-*octylisoxazole* **(80b)**.

To a stirred solution of hydroxylamine hydrochloride (2.44 g, 35 mmol) in pyridine (50 ml), at room temperature, was added a solution of 3-formyl-5-octylisoxazole **(79b)** (4.21 g, 23 mmol) in pyridine (10 ml). After stirring for 90 minutes the reaction mixture was concentrated *in vacuo*, dissolved in ethyl acetate (50 ml) and washed with 10% aqueous HCl (3 x 60 ml), water (100 ml), then dried over $MgSO_4$. Evaporation of the solvent *in vacuo* gave a white solid which was recrystallised from hexane, furnishing the title oxime **(80b)** as a white powder (4.07 g, 89%), (5:1 mixture of isomers) m.p. 79-89°C (Found: C, 64.0; H, 9.05; N, 12.04. $C_{12}H_{20}N_2O_2$ requires C, 64.25; H, 8.99; N, 12.49%); $\nu_{max.}$ (Nujol) 3230 (O-

H), 1595 cm^{-1} (C=N); δ_H (200 MHz; $CDCl_3$) 10.26, 9.75[1] (1H, br.s, OH), 8.26[1], 7.68 (1H, s, HON=C*H*), 6.75, 6.32[1] (1H, s, H_4), 2.72 (2H, t, α-CH_2), 1.7-1.0 (12H, br.m, 6XCH_2), 0.84 (3H, br.t, CH_3); δ_C (50MHz; $CDCl_3$) 174.3, 157.7 (C_3, C_5), 141.2 (HON=*C*H), 97.8 (C_4), 31.6, 28.9, 27.2, 26.4, 22.4 (CH_2s), 13.9 (CH_3); m/z 224 (*M*+, 4%), 141 (19), 126 (37), 71 (20).

1. Major isomer.

3.9.14. 3-*aldoximino*-5-*phenyl*-2-*isoxazoline* (**80c**).

To a stirred solution of hydroxylamine hydrochloride (1.78 g, 25.7 mmol) in pyridine (40 ml) was added a solution of 3-formyl-5-phenyl-2-isoxazoline (**79c**) (2.9 g, 16.5 mmol) in pyridine (5 ml). After stirring at room temperature for 1 hour the reaction mixture was poured into water (100 ml) and extracted with ethyl acetate (3 x 60 ml). The combined organic extract was washed with 5% aqueous HCl (3 x 60 ml), dried over $MgSO_4$ and the solvent evaporated *in vacuo* to leave a white solid, which was pure by tlc (EtOAc/hexane, 1:4). An analytical sample was obtained by Kugelrohr distillation of a portion of the product (120°C, 0.05 mmHg), m.p. 86-88°C (Found: C, 63.1; H, 5.30; N, 14.60. $C_{10}H_{10}N_2O_2$ requires C, 63.14; H, 5.30; N, 14.73%); (Found: *M*+,190.0743. $C_{10}H_{10}N_2O_2$ requires *M*, 190.07422); $\nu_{max.}$ (Nujol) 3180 cm^{-1} (O-H); δ_H (200 MHz; $CDCl_3$) 9.37 (1H, br.s, OH), 8.15 (1H, s, HON=C*H*), 7.5-7.25 (5H, m, ArH), 5.66 (1H, dd, J_{H5H4a} 11.1 Hz, J_{H5H4b} 8.6 Hz, H_5), 3.56 (1H, dd, J_{H4aH4b} 17.3 Hz, J_{H4aH5} 11.1 Hz, H_{4a}), 3.15 (1H, dd, J_{H4bH4a} 17.3 Hz, J_{H4bH5} 8.6 Hz, H_{4b}); δ_C (50 MHz; $CDCl_3$) 154.1 (C_3), 142.7 (HON=*C*H), 139.7 (PhC), 128.7, 128.4, 125.8 (PhCH), 83.4 (C_5), 40.6 (C_4); m/z 190 (*M*+, 100%), 173 (27), 115 (21), 104 (81), 77 (29).

3.9.15. *3-aldoximino-5-octyl-2-isoxazoline* **(80d).**

3.9.15.1. Preparation Using Pyridine as the Solvent.

To a stirred solution of hydroxylamine hydrochloride (0.82 g, 12.7 mmol) in pyridine (20 ml), at room temperature, was added a solution of 3-formyl-5-octyl-2-isoxazoline **(79d)** (1.79 g, 8.46 mmol) in pyridine (15 ml). After stirring for 90 minutes the reaction mixture was poured into water (50 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic extract was washed with 10% aqueous HCl (3 x 50 ml), water (50 ml), brine (50 ml), then dried over $MgSO_4$ and the solvent evaporated *in vacuo* to give a white solid. Recrystallisation from cyclohexane furnished a white powder (1.54 g, 81%) m.p. 100-102°C, δ_H (200 MHz; $(CD_3)_2CO$) 10.95 (1H, s, OH), 7.98 (1H, s, HON=C*H*), 4.73-4.57 (1H, m, H_5), 3.22 (1H, dd, J_{H4aH4b} 17.1 Hz, J_{H4aH5} 10.4 Hz, H_{4a}), 2.77 (1H, dd, J_{H4bH4a} 17.1 Hz, J_{H4bH5} 8.4 Hz, H_{4b}), 1.71-1.19 (14H, br.m, 7xCH_2), 0.88 (3H, t, CH_3); δ_C (50 MHz; $(CD_3)_2CO$) 153.7 (C_3), 141.1 (HON=*C*H), 81.2 (C_5), 37.0 (C_4), 34.2, 30.9, 24.5, 21.6 (CH_2s), 12.6 (CH_3); m/z 226 (*M*$^+$, 9%), 113 (*M*-113, 100%).

3.9.15.2. Preparation Using a Two Phase System.

To a solution of hydroxylamine hydrochloride (1.65 g, 23 mmol) and sodium hydroxide (0.94 g, 23 mmol) in water (5 ml) was added a solution of 3-formyl-5-octyl-2-isoxazoline **(79d)** (1.0 g, 4.7 mmol) in ether. After stirring vigorously for 5 minutes a thick white precipitate formed; chloroform (100 ml) was added to dissolve it. After 2 hours tlc (EtOAc/hexane, 1:4) showed aldehyde remaining, a second equivalent of hydroxylamine hydrochloride and sodium hydroxide was added in water (15 ml) and stirred for 2 days at which time the reaction was complete. The organic layer was separated and washed with water (2 x 50 ml), brine (50 ml), dried over $MgSO_4$ and the solvent evaporated *in vacuo* to

yield a white solid. Recrystallisation from cyclohexane furnished a white powder (0.83 g, 77%) (63:37 mixture of isomers) m.p. 89.5-91°C (Found: C, 63.7; H, 10.0; N, 12.40. $C_{12}H_{22}N_2O_2$ requires C, 63.7; H, 9.8; N, 12.38%); $\nu_{max.}$ (Nujol) 3200 cm^{-1} (O-H); δ_H (80 MHz; $(CD_3)_2CO$) 10.85 (1H, br.s, OH), 7.96 (0.63H, s, HON=C*H*), 7.27 (0.37H, s, HON=C*H*), 4.76-4.45 (1H, m, H_5), 3.76-2.57 (2H, m, H_{4a}, H_{4b}), 1.73-1.02 (14H, br.m, 7xCH_2), 0.87 (1H, t, CH_3); δ_C (50 MHz; $(CD_3)_2CO$) 153.6 (C_3), 140.8, 140.7 (HON=*C*H), 80.9 (C_5), 36.7 (C_4), 34.1, 30.8, 24.4, 21.5, (CH_2s), 12.6 (CH_3); m/z 226 (*M*+, 10%), 209 (14), 113 (100), 87 (10).

3.9.16. 3-*aldoximino*-4,5-*dibutylisoxazole* **(80e).**

To a stirred solution of hydroxylamine hydrochloride (0.31 g, 4.4 mmol) in pyridine (5 ml), at room temperature, was added a solution of 4,5-dibutyl-3-formylisoxazole **(79e)** (0.75 g, 3.6 mmol) in pyridine (5 ml). After stirring for 30 minutes the reaction mixture was poured into ether (50 ml) and washed with water (2 x 40 ml), 5% aqueous HCl (30 ml), dried over $MgSO_4$ and the solvent evaporated *in vacuo,* leaving a white solid. Recrystallisation from hexane furnished the title oxime **(80e)** as fine white needles (0.64 g, 79%), m.p. 84.5-85.5°C (Found: C, 64.0; H, 9.06; N, 12.3. $C_{12}H_{20}N_2O_2$ requires C, 64.29; H, 8.93; N, 12.5%); $\nu_{max.}$ (Nujol) 3220 (O-H), 1620 cm^{-1} (C=N); δ_H (80 MHz; $CDCl_3$) 8.74 (1H, br.s, OH), 8.22 (1H, s, HON=C*H*), 2.76-2.40 (4H, br.m, 2xα-CH_2s), 1.66-1.13 (8H, m, 4xCH_2), 1.0-0.81 (6H, m, 2xCH_3); δ_C (50 MHz; $CDCl_3$) 169.9, 156.1 (C_3, C_5), 142.3 (HON=*C*H), 113.3 (C_4), 31.7, 29.5, 24.7, 22.1, 21.9, (CH_2s),13.6, 13.4 (2xCH_3); m/z 224 (*M*+, 2%), 206 (23), 163 (41), 135 (14), 121 (100), 85 (48).

3.9.17. Attempted Rearrangement of 3-aldoximino-5-phenylisoxazole (**80a**).[136]

To a stirred solution of the title oxime (**80a**) (0.66 g, 3.5 mmol) in ethanol (10 ml) was added 20% aqueous potassium hydroxide solution (3 ml). After refluxing for 105 minutes the reaction was cooled to room temperature and concentrated *in vacuo*. The residual yellow oil was diluted with water and adjusted to pH 5 with aqueous hydrochloric acid, then extracted with ethyl acetate (3 x 20 ml). The combined organic extract was dried over $MgSO_4$ and the solvent evaporated under reduced pressure furnishing an off-white solid (0.65 g, 98%) which was shown by tlc (Et_2O/hexane, 1:1) and ^{1}H-NMR to be starting material. δ_H (80 MHz; $(CD_3)_2CO$) 11.1 (1H, br.s, OH), 8.23 (1H, d, $J_{H3\alpha H4}$ 0.4 Hz, $H_{3\alpha}$), 7.95-7.83 (2H, m, ArH), 7.58-7.45 (3H, m, ArH), 7.03 (1H, d, $J_{H4H3\alpha}$ 0.4 Hz, H_4).

3.10. Cycloaddition Reactions of Isoxazole- and 2-Isoxazoline-3-carbonitrile Oxides.

Four approaches to the generation of these heterocyclic nitrile oxides were investigated: 1) chlorination with chlorine gas followed by dehydrochlorination of the isolated hydroximoyl chloride; 2) chlorination-dehydrochlorination in the presence of chloramine-T; 3) treatment with sodium hypochlorite solution; 4) reaction with *N*-chlorosuccinimide followed by triethylamine.

3.10.1. Use of Chlorine Gas to Generate the Hydroximoyl Chlorides.

3.10.1.1. Attempted Chlorination of 3-aldoximino-5-phenylisoxazole (**80a**).

Chlorine gas was bubbled through a solution of (**80a**) (0.1 g, 0.53 mmol) in chloroform (5 ml), which had been cooled to *ca.* -5°C, for 10 minutes.

When all of the starting material had been consumed, (tlc, light petrol/Et_2O, 1:1) nitrogen was passed through the solution for 5 minutes then the solvent evaporated *in vacuo*. Preparative tlc (Et_2O/hexane, 1:1) furnished two components (6 mg of each) which were not identified.

3.10.1.2. Chlorination of 3-aldoximino-4,5-dibutylisoxazole **(80e)**.[139]

To a solution of chlorine (*ca.* 71 mg, 0.1 mmol) in dry chloroform (13 ml) was added the 3-aldoximino-4,5-dibutylisoxazole **(80e)** (100 mg, 0.46 mmol). After stirring overnight no oxime remained by tlc (Et_2O/hexane, 1:1). The solvent was evaporated *in vacuo* yielding a yellowish oil ($\nu_{max.}$ (neat) 3250 (O-H), 760 cm^{-1} (C-Cl)).

Treatment of a small portion of the oil with triethylamine in ether gave rise to a precipitate ($Et_3N^+HCl^-$) which was filtered off; concentration of the filtrate *in vacuo* left an oil ($\nu_{max.}$ (neat) 1620 cm^{-1} ($C{=}NO_2$, furoxan).[140]

The remainder of the oil (120 mg) was dissolved in ether (6 ml), and hex-1-ene (170 mg, 2 mmol) added. A solution of triethylamine (60 mg, 0.6 mmol) in ether (5 ml) was added over 7 hours. The reaction mixture was filtered through Celite and the filtrate concentrated *in vacuo*. Preparative tlc (Et_2O/light petrol, 1:3) afforded an oil (81 mg) ^{1}H-NMR suggests that the isoxazoline adduct is present along with some impurities.

3.10.2. Use of Chloramine-T for *in situ* Nitrile Oxide Generation.[41]

3.10.2.1. 5-*butyl*-3-(5-*phenylisoxazol*-3-*yl*)-2-*isoxazoline* **(83)**.

A solution of 3-aldoximino-5-phenylisoxazole **(80a)** (0.25 g, 1.33 mmol), hex-1-ene (0.33 g, 3.99 mmol) and chloramine-T (0.41 g, 1.45 mmol) in dry methanol (25 ml) was refluxed for 3.5 hours. Tlc (Et_2O/hexane, 1:1) at this stage showed incomplete consumption of the oxime. A further

equivalent of chloramine-T (0.41 g, 1.45 mmol) was added, and refluxing continued for a further 3 hours. The reaction mixture was poured into water (60 ml) and extracted with dichloromethane (4 x 30 ml). The combined organic extract was washed with water (50 ml), 1 molar aqueous sodium hydroxide (2 x 30 ml), again with water (50 ml), then dried over $MgSO_4$, and the solvent evaporated *in vacuo*. The residue was subjected to dry flash chromatography (Et_2O/hexane, 1:9) furnishing the title adduct (**83**) as a white solid (0.136 g, 38%), m.p. 101-102.5°C (from hexane) (Found: C, 70.9; H, 6.74; N, 10.4. $C_{16}H_{18}N_2O_2$ requires C, 71.11; H, 6.67; N, 10.37%); (Found: M^+, 270.1366. $C_{16}H_{18}N_2O_2$ requires *M*, 270.13682); δ_H (80 MHz; $CDCl_3$) 7.83-7.71 (2H, m, ArH), 7.50-7.37 (3H, m, ArH), 6.90 (1H, s, H_4), 5.0-4.6 (1H, m, H_5), 3.48 (1H, dd, J_{H4aH4b} 17.2 Hz, J_{H4aH5} 10.3 Hz, H_{4a}), 3.03 (1H, dd, J_{H4bH4a} 17.2 Hz, J_{H4bH5} 8.6 Hz, H_{4b}), 1.8-1.2 (6H, m, $3xCH_2$), 0.91 (3H, br.t, CH_3); δ_C (50MHz; $CDCl_3$) 170.3,156.0 (C_3, $C_{5\ isoxazole}$), 149.4 ($C_{3\ isoxazoline}$), 130.4, 128.9, 126.7, 125.8 (Ph), 97.2 ($C_{4\ isoxazole}$), 82.6 ($C_{5\ isoxazoline}$), 38.7 ($C_{4\ isoxazoline}$), 34.7, 27.3, 22.3 ($3xCH_2$), 13.8 (CH_3); m/z 270 (M^+, 62%), 213 (89), 185 (78), 116 (25), 105 (100).

3.10.2.2. *5-octyl*-3-(*5-octylisoxazol*-3-*yl*)-2-*isoxazoline* (**84**).

A solution of 3-aldoximino-5-octylisoxazole (**80b**) (0.75 g, 3.35 mmol), dec-1-ene (1.41 g, 10 mmol) and chloramine-T (2.24 g, 8.0 mmol) in dry ethanol was stirred under reflux for 14 hours. The reaction mixture was then poured into water (150 ml) and extracted with ether (3 x 50 ml). The combined organic extracts were washed with water (100 ml) then dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The residue was subjected to flash column chromatography (hexane then Et_2O/hexane, 2:98). The resulting white solid was recrystallised from hexane furnishing

the title compound **(84)** as a white powder (0.162 g, 13%), m.p. 60-61°C, δ_H (80 MHz; $CDCl_3$) 6.37 (1H, $J_{H4(5\alpha-CH2)}$ 0.7 Hz, $H_{4\ isoxazole}$), 4.95-4.52 (1H, m, $H_{5\ isoxazoline}$), 3.41 (1H, dd, J_{H4aH4b} 17.1 Hz, J_{H4aH5} 10.3 Hz, $H_{4a\ isoxazoline}$), 2.96 (1H, dd, J_{H4bH4a} 17.1 Hz, J_{H4bH5} 8.6 Hz, $H_{4b\ isoxazoline}$), 2.74 (2H, br.t, J 7.2 Hz, 5α-CH_2), 1.77-1.01 (26H, br.m, 13xCH_2), 0.85 (6H, br.t, 2xCH_3); δ_C (50 MHz, $CDCl_3$) 174.3, 155.4 (C_3, $C_{5\ isoxazole}$), 149.6 ($C_{3\ isoxazoline}$), 98.6 ($C_{4\ isoxazole}$), 82.4 ($C_{5\ isoxazoline}$), 38.8 ($C_{4\ isoxazoline}$), 35.0, 31.7, 29.3, 29.0, 28.9, 27.3, 26.4, 25.2, 22.5 (CH_2s), 13.9 (CH_3).

3.10.3. Use of Sodium Hypochlorite Solution for *in situ* Nitrile Oxide Generation.[35]

3.10.3.1. 5-*phenyl*-3-(5-*phenylisoxazole*-3-*yl*)-2-*isoxazoline* **(86)**.

To a solution of 3-aldoximino-5-phenylisoxazole **(80a)** (0.5 g, 2.66 mmol), triethylamine (13 mg, 0.13 mmol) and styrene (0.55 g, 5.32 mmol) in chloroform (20 ml) was added aqueous sodium hypochlorite solution (*ca.* 0.4 M, 2.7 mmol, 6.75 ml). After stirring vigorously for 3 hours tlc (EtOAc/hexane, 1:3) showed unconsumed oxime; a further portion of sodium hypochlorite solution was added (3.5 ml, 1.4 mmol). After stirring for a further 45 minutes no oxime remained. Water (20 ml) was added to the reaction mixture and the organic phase separated, the aqueous portion was extracted with chloroform (20 ml). The combined organic extract was washed with water (50 ml), then dried over $MgSO_4$ and the solvent evaporated *in vacuo*, yielding a yellowish solid which was recrystallised from ethanol, furnishing the title adduct **(86)** as white needles (0.37 g, 48%), m.p. 143-144°C; (Found: C, 74.3; H, 4.86; N, 9.65. $C_{18}H_{14}N_2O_2$ requires C, 74.46; H, 4.86; N, 9.65%); δ_H (80MHz; $CDCl_3$) 7.85-7.73 (2H, m, ArH); 7.51-7.32 (8H, m, ArH); 6.98 (1H, s, $H_{4\ isoxazole}$),

5.80 (1H, dd, J_{H5H4a} 10.9 Hz, J_{H5H4b} 8.9 Hz, $H_{5\ isoxazoline}$), 3.88 (1H, dd, J_{H4aH4b} 17.4 Hz, J_{H4aH5} 10.9 Hz, $H_{4a\ isoxazoline}$), 3.42 (1H, dd, J_{H4bH4a} 17.4 Hz, J_{H4bH5} 8.9 Hz, $H_{4b\ isoxazoline}$); δ_C (50 MHz; $CDCl_3$) 170.3, 155.5 (C_3, $C_{5\ isoxazole}$), 149.2 ($C_{3\ isoxazoline}$), 139.7 (PhC), 130.3, 128.8, 128.6, 128.2, 125.7_1, 125.6_8 (PhCH), 126.5 (PhC), 97.2 ($C_{4\ isoxazole}$), 83.4 ($C_{5\ isoxazoline}$), 41.5 ($C_{4\ isoxazoline}$); m/z 290 (*M*+, 27%), 128 (11), 115 (21), 104 (100).

3.10.3.2. 5-butyl-3-(5-phenylisoxazol-3-yl)-2-isoxazoline **(83)**.

To a solution of 3-aldoximino-5-phenylisoxazole **(80a)** (0.2 g, 1.06 mmol) and hex-1-ene (0.89 g, 10.6 mmol) in dichloromethane (4 ml) was added an aqueous solution of sodium hypochlorite (*ca.* 0.3 M, 3.7 ml, 1.1 mmol). After stirring vigorously for 4 hours tlc (Et_2O/hexane, 3:7) showed unconsumed oxime; a further portion of hypochlorite solution was added (4 ml, 1.17 mmol); after stirring overnight a third portion of oxidant solution was added (2 ml, 0.58 mmol). After 3 hours, water (20 ml) was added and the organic phase separated; the aqueous layer was extracted with dichloromethane (3 x 30 ml), and the combined organic extract dried over $MgSO_4$. The solution was concentrated *in vacuo* and the product precipitated by the addition of light petrol. The solid was filtered and recrystallised from hexane furnishing a white solid (0.09 g, 31%), m.p. 99-100.5°C, δ_H (80 MHz; $CDCl_3$) 7.85-7.70 (2H, m, ArH), 7.54-7.24 (3H, m, ArH), 6.91 (1H, s, $H_{4\ isoxazole}$), 4.92-4.60 (1H, m, $H_{5\ isoxazoline}$), 3.48 (1H, dd, J_{H4aH4b} 17.2 Hz, J_{H4aH5} 10.3 Hz, $H_{4a\ isoxazoline}$), 3.03 (1H, dd, J_{H4bH4a} 17.2 Hz, J_{H4bH5} 8.6 Hz, $H_{4b\ isoxazoline}$), 1.86-1.16 (6H, m, $3xCH_2$), 0.91 (3H, t, CH_3), δ_C (50MHz; $CDCl_3$) 170.3, 156.0 (C_3, $C_{5\ isoxazole}$), 149.4 ($C_{3\ isoxazole}$), 130.4, 128.9, 125.8 (PhCH), 126.7 (PhC), 97.2 ($C_{4\ isoxazole}$), 82.6 ($C_{5\ isoxazoline}$), 38.7 ($C_{4\ isoxazoline}$), 34.7, 27.3, 22.3 ($3xCH_2$), 13.8 (CH_3); m/z 270 (*M*+, 47%), 213 (78), 185 (79), 116 (24), 105 (100), 77 (56).

3.10.3.3. *5-octyl-3-(5-phenylisoxazol-3-yl)-2-isoxazoline* **(85).**

To a stirred solution of 3-aldoximino-5-phenylisoxazole **(80a)** (0.5 g, 2.66 mmol), dec-1-ene (0.75 g, 5.32 mmol) and triethylamine (20 mg, 0.19 mmol) in chloroform (20 ml) was added aqueous sodium hypochlorite solution (*ca.* 0.4 M, 11.75 ml, 4.7 mmol). After stirring vigorously overnight there was still some unreacted oxime (tlc, EtOAc/hexane, 1:4). A second portion of sodium hypochlorite was added (11.75 ml, 4.75 mmol). After stirring for a further 2 hours the organic layer was separated and the aqueous portion extracted with chloroform (50 ml). The combined organic extract was washed with water (2 x 50 ml), then dried over $MgSO_4$ and the solvent evaporated *in vacuo* affording a white solid. Flash column chromatography (Et_2O/hexane, 1:19) followed by recrystallisation from ethanol furnished the product **(85)** as a white amorphous solid (0.45 g, 51%), m.p. 98.5-99.5°C (Found: C, 73.6; H, 8.21; N, 8.54. $C_{20}H_{26}N_2O_2$ requires C, 73.58; H, 8.03; N, 8.58%); δ_H (200 MHz; $CDCl_3$) 7.82-7.75 (2H, m, ArH), 7.50-7.25 (3H, m, ArH), 6.92 (1H, s, $H_{4\ isoxazole}$), 4.83-4.71 (1H, m, $H_{5\ isoxazoline}$), 3.46 (1H, dd, J_{H4aH4b} 17.2 Hz, J_{H4aH5} 10.6 Hz, $H_{4a\ isoxazoline}$), 3.05 (1H, dd, J_{H4bH4a} 17.2 Hz, J_{H4bH5} 8.4 Hz, $H_{4b\ isoxazoline}$), 1.86-1.12 (14H, br.m, 7xCH_2) 0.86 (3H, t, CH_3); δ_C (50 MHz; $CDCl_3$) 170.2, 156.0 (C_3, $C_{5\ isoxazole}$), 149.4 ($C_{3\ isoxazoline}$), 130.4, 128.9, 125.7 (PhCH), 126.7 (PhC), 97.2 ($C_{4\ isoxazole}$), 82.6 ($C_{5\ isoxazoline}$), 38.7 ($C_{4\ isoxazoline}$), 35.0, 31.7, 29.3, 25.2, 22.5 (CH_2s), 14.0 (CH_3); m/z 326 (M^+, 5%), 213 (96), 185 (38), 116 (16), 105 (100), 77 (58).

3.10.3.4 *5-(pyrid-2-yl)-3-(5-phenylisoxazol-3-yl)-2-isoxazoline* **(87).**

To a stirred solution of 3-aldoximino-5-phenylisoxazole **(80a)** (0.5 g, 2.66 mmol) and 2-vinylpyridine (0.56 g, 0.57 ml, 5.32 mmol) in dichloromethane (20 ml), was added a solution of commercial sodium

hypochlorite (5% available chlorine) (40 ml). After stirring for 1 hour the reaction mixture was poured into ether (70 ml) and the organic layer separated. The aqueous portion was extracted with ether (2 x 30 ml), and the combined organic extract washed with brine (80 ml), dried over $MgSO_4$ and the solvent evaporated *in vacuo* to yield a white solid. Flash column chromatography (EtOAc/hexane, 1:4 then 1:1) furnished two components, which were in order of elution: 4,5-di-(5-phenylisoxazol-3-yl)furazan-*N*-oxide **(65)** (0.155 g, 31%), m.p. 177-181°C (from benzene/ethanol) (lit.,[129] 188°C), δ_H (80 MHz; $CDCl_3$) 7.89-7.70 (4H, m, ArH), 7.49-7.36 (6H, m, ArH), 7.28 (1H, s, H_4), 7.15 (1H, s, $H_{4'}$); and the title adduct **(87)** (0.324 g, 44%), m.p. 135-136°C (from ethanol), (Found: C, 70.01; H, 4.47; N, 14.40. $C_{17}H_{13}N_2O_2$ requires C, 70.09; H, 4.50; N, 14.42%); δ_H (300 MHz; $CDCl_3$) 8.6-8.55 (1H, m, Py-H_6), 7.82-7.78 (2H, m, ArH), 7.76-7.70 (1H, m, Py-H_4), 7.53-7.46 (4H, m, ArH & Py-H_3), 7.28-7.23 (1H, m, Py-H_5), 6.97 (1H, s, $H_{4\ isoxazole}$), 5.91 (1H, dd, J_{H5H4a} 10.9 Hz, J_{H5H4b} 7.8 Hz, $H_{5\ isoxazoline}$), 3.91 (1H, dd, J_{H4aH4b} 17.5 Hz, J_{H4aH5} 10.9 Hz, $H_{4a\ isoxazoline}$), 3.82 (1H, dd, J_{H4bH4a} 17.5 Hz, J_{H4bH5} 7.8 Hz, $H_{4b\ isoxazoline}$); δ_C (75 MHz; $CDCl_3$) 170.5, 155.5 (C_3, $C_{5\ isoxazole}$), 155.2 (Py-C_2), 149.5 ($C_{3\ isoxazoline}$), 149.1 (Py-C_6), 136.5 (Py-C_4), 130.1 (Py-C_3), 128.6, 125.4, 120.3 (PhCH), 122.7 (PhC), 97.0 ($C_{4\ isoxazole}$), 83.0 ($C_{5\ isoxazoline}$), 39.8 ($C_{4\ isoxazoline}$); m/z 291 (*M*+, 4%), 274 (34), 261 (100), 213 (25), 117 (21), 105 (57).

3.10.3.5. *5-butyl-3-(5-octylisoxazol-3-yl)-2-isoxazoline* **(89).**

To a stirred solution of 3-aldoximino-5-octylisoxazole **(80b)** (0.10 g, 0.45 mmol) and hex-1-ene (0.37 g, 4.6 mmol) in dichloromethane (2 ml) was added aqueous sodium hypochlorite (*ca.* 0.3 M, 0.9 mmol, 3.0 ml). After stirring vigorously for 1 hour a further portion of hypochlorite solution (0.5

ml) was added and stirring continued for a further 30 minutes. The reaction mixture was then poured into water and extracted with dichloromethane (3 x 20 ml). The combined organic extract was dried over $MgSO_4$, and the solvent evaporated *in vacuo* to yield a yellow oil. Dry flash chromatography (Et_2O/hexane, 3:97 then 5:95) furnished a white solid which was recrystallised from methanol to give the title adduct **(89)** (0.07 g, 51%), m.p. 53-54°C (Found: C, 70.80; H, 10.10; N, 9.40. $C_{18}H_{30}N_2O_2$ requires C, 70.54; H, 9.87; N, 9.14%); δ_H (80 MHz; $CDCl_3$) 6.39 (1H, s, $H_{4\ isoxazole}$), 4.84-4.68 (1H, m, $H_{5\ isoxazoline}$), 3.42 (1H, dd, J_{H4aH4b} 17.2 Hz, J_{H4aH5} 10.5 Hz, $H_{4a\ isoxazoline}$), 3.01 (1H, dd, J_{H4bH4a} 17.2 Hz, J_{H4bH5} 8.3 Hz, $H_{4b\ isoxazoline}$), 2.75 (2H, t, J 7.4 Hz, 5α-CH_2), 1.8-1.26 (18H, br.m, 9xCH_2), 0.94-0.83 (6H, 2t, 2XCH_3); δ_C (50 MHz; $CDCl_3$) 174.4, 155.4 (C_3, $C_{5\ isoxazole}$), 149.6 ($C_{3\ isoxazoline}$), 98.7 ($C_{4\ isoxazole}$), 82.4 ($C_{5\ isoxazoline}$), 38.8 ($C_{4\ isoxazoline}$), 34.7, 31.7, 29.0, 28.9, 27.3, 26.5, 22.5, 22.4 (CH_2s), 13.9, 13.8 (2xCH_3); m/z (FAB ms) 307 [(M+H)$^+$].

3.10.3.6. 5-(*pyrid*-2-*yl*)-3-(5-*octylisoxazol*-3-*yl*)-2-*isoxazoline* **(88).**

To a stirred solution of 3-aldoximino-5-octylisoxazole **(80b)** (0.50 g, 2.23 mmol) and 2-vinylpyridine (0.47 g, 0.48 ml, 4.46 mmol) in dichloromethane (20 ml) was added dropwise, over 10 minutes, a solution of sodium hypochlorite (commercial, 5% available chlorine) (40 ml). After 3 hours the reaction mixture was poured into water (50 ml) and extracted with ether (3 x 40 ml); the combined organic extract was washed with brine (50 ml), dried over $MgSO_4$, and the solvent evaporated *in vacuo*. The residue was subjected to flash column chromatography (EtOAc/hexane, 1:4) which furnished the title compound as a clear oil (0.55 g, 75%). A portion of the product was converted to the hydrochloride salt (ethereal HCl) which was recrystallised from Et_2O/EtOH to provide an

analytical sample, m.p. 140-145°C (Found: C, 62.71; H, 7.22; H, 11.52. $C_{19}H_{26}ClN_3O_2$ requires C, 62.71; H, 7.20; N, 11.55%); (the rest of the analytical data was obtianed for the free base) δ_H (300 MHz; $CDCl_3$) 8.60 1H, d, *J* 4.7 Hz, Py-H_6), 7.74-7.69 (1H, m, Py-H_4), 7.49 (1H, d, *J* 7.7 Hz, Py-H_3) 7.26-7.22 (1H, m, Py-H_5), 6.43 (1H, s, $H_{4\ isoxazole}$), 5.87 (1H, dd, J_{H5H4a} 11.0 Hz, J_{H5H4b} 7.6 Hz, $H_{5\ isoxazoline}$), 3.86 (1H, dd, J_{H4aH4b} 17.6 Hz, J_{H4aH5} 11.0 Hz, $H_{4a\ isoxazoline}$), 3.76 (1H, dd, J_{H4bH4a} 17.6 Hz, J_{H4bH5} 7.6 Hz, $H_{4b\ isoxazoline}$), 2.77 (2H, t, *J* 7.5 Hz, 5α-CH_2), 1.71 (2H, t, *J* 7.5 Hz, 5β-CH_2), 1.32-1.27 (10H, m, 5xCH_2), 0.89 (3H, t, *J* 6.9 Hz, CH_3); δ_C (75 MHz; $CDCl_3$) 174.4, 154.8 (C_3, $C_{5\ isoxazole}$), 158.8 (Py-C_2)), 149.9 ($C_{3\ isoxazoline}$), 149.4 (Py-C_6), 136.7 (Py-C_4), 122.9, 120.6 (Py-C_3, C_5), 98.7 ($C_{4\ isoxazole}$), 83.1 ($C_{5\ isoxazoline}$), 40.2 ($C_{4\ isoxazoline}$), 31.6, 28.9, 28.8, 27.2, 26.4, 22.4 (CH_2s), 13.9 (CH_3); m/z 327 (*M*+, 6%), 297 (100), 249 (34), 156 (15), 121 (20).

3.10.3.7. *5-butyl-3-(4,5-dibutylisoxazol-3-yl)-2-isoxazoline* **(82).**

To a stirred solution of 3-aldoximino-4,5-dibutylisoxazole **(80e)** (0.10 g, 0.45 mmol) and hex-1-ene (0.337 g, 4.6 mmol) in dichloromethane (2 ml) was added aqueous sodium hypochlorite solution (*ca.* 0.3 M, 1.05 mmol, 3.5 ml). After 6 hours tlc (Et_2O/hexane, 3:17) showed a small amount of oxime remaining. A second portion of hypochlorite solution was added (1.0 ml). After stirring for a further 1 hour the reaction mixture was poured into water (20 ml) and extracted with dichloromethane (3 x 20 ml).The combined organic extract was dried over $MgSO_4$ and then the solvent evaporated *in vacuo*. The residue was subjected to flash column chromatography (Et_2O/hexane, 3:97) which furnished the cycloadduct **(82)** as a clear oil (0.128 g, 93%), (Found: *M*+, 306.2301. $C_{18}H_{30}N_2O_2$

requires *M*, 306.23071); δ_H (200 MHz; $CDCl_3$) 4.67 (1H, dddd, J_{H5H4a} 10.5 Hz, J_{H5H4b} 8.4 Hz, $J_{H5CH2\text{-}5\alpha}$ 6.8 and 5.8 Hz, H_5), 3.43 (1H, dd, J_{H4aH4b} 17.1 Hz, J_{H4aH5} 10.5 Hz, H_{4a}), 3.02 (1H, dd, J_{H4bH4a} 17.1 Hz, J_{H4bH5} 8.4 Hz, H_{4b}), 2.68 (2H, t, 5α-CH_2), 2.55 (2H, dt, 4α-CH_2), 1.72-1.23 (14H, m, 7xCH_2), 0.95-0.85 (9H, m, 3xCH_3); δ_C (50 MHz; $CDCl_3$) 169.9, 154.4 (C_3, C_5 isoxazole), 150.3 (C_3 isoxazoline), 113.8 (C_4 isoxazole), 81.2 (C_5 isoxazoline), 39.9 (C_4 isoxazoline), 34.7, 31.8, 29.6, 27.4, 24.8, 22.3, 22.1 (CH_2s), 13.7, 13.5 (CH_3s); m/z 306 (*M*+, 20%), 277 (69), 249 (100), 179 (19), 165 (10), 138 (11).

3.10.3.8. 5-(*pyrid*-2-*yl*)-3-(5-*phenyl*-2-*isoxazolin*-3-*yl*)-2-*isoxazoline* **(90).**

To a stirred solution of 3-aldoximino-5-phenyl-2-isoxazoline **(80c)** (0.655 g, 3.45 mmol) and 2-vinylpyridine (0.72 g, 0.74 ml, 6.89 mmol) in dichloromethane (20 ml) was added in a dropwise manner a solution of sodium hypochlorite (commercial, 5% available chlorine) (30 ml). The reaction was stirred for 20 minutes after completion of the addition, then poured into water (30 ml) and extracted with dichloromethane (3 x 30 ml). The combined organic extract was dried over $MgSO_4$ and then the solvent evaporated *in vacuo*. The residue was flash column chromatographed (EtOAc/hexane, 3:7 then 1:1) furnishing two components: a mixture (*RR/SS*)- and (*RS/SR*)-3,4-di-(5-phenyl-2-isoxazolin-3-yl)furazan-*N*-oxide **(91)** (0.136 g, 21%), δ_H (300 MHz; $CDCl_3$) 7.4-7.25 (10H, m, ArH), 5.84 (2H, dd, J_{H5H4a} 8.9 Hz, J_{H5H4b} 6.3 Hz, H_5, both isomers), 5.81 (2H, dd, $J_{H5'H4a'}$ 8.9 Hz, $J_{H5'H4b'}$ 6.3 Hz, $H_{5'}$ both isomers), 3.89-3.84 (4H, m, H_{4a} & $H_{4a'}$, both isomers), 3.53-3.17 (4H, m, H_{4b} & $H_{4b'}$, both isomers); m/z 376 (*M*+, 6%), 254 (4), 172 (20), 128 (13), 107 (36), 104 (100), 91 (22), 77 (62):

a mixture of (RR/SS)- and (RS/SR)-5-(*pyrid*-2-*yl*)-3-(5-*phenyl*-2-*isoxazolin*-3-*yl*)-2-*isoxazoline* (**90**), (0.504 g, 50%) (Found: C, 69.41; H, 5.12; N, 14.26. $C_{17}H_{15}N_3O_2$ requires C, 69.61; H, 5.15; N, 14.33%); δ_H (300 MHz; $CDCl_3$) 8.61 (1H, d, *J* 4.8 Hz, Py-H_6), 7.75-7.69 (1H, m, Py-H_4), 7.46 (1H, d, *J* 7.8 Hz, Py-H_3), 7.41-7.31 (5H, m, ArH). 7.27-7.22 (1H, m, Py-H_5), 5.83 (1H, dd, $J_{H5'H4a'}$ 10.5 Hz, $J_{H5'H4b'}$ 8.2 Hz, $H_{5'}$), 5.72 (1H, dd, J_{H5H4a} 11.1 Hz, J_{H5H4b} 8.6 Hz, H_5), 3.82-3.67 (3H, m, H_{4a}, $H_{4a'}$, $H_{4b'}$), 3.33 (1H, dd, J_{H4bH4a} 17.3 Hz, J_{H4bH5} 8.6 Hz, H_{4b}); δ_C (75 MHz; $CDCl_3$) 159.4 (Py-C_2), 151.0, 150.4 (C_3, $C_{3'}$), 149.5 (Py-C_6), 139.7 (PhC), 136.8 (Py-C_4), 128.6, 128.3, 125.7 (PhCH), 123.1, 120.8 (Py-C_3 & C_5), 83.7, 83.6 (C_5, $C_{5'}$), 41.4 (C_4), 39.8 ($C_{4'}$); m/z 293 (*M*+, 15%), 276 (52), 263 (100).

3.10.4. Use of *N*-chlorosuccinimide (NCS) for *in situ* Nitrile Oxide Generation.[40]

General Procedure.

To a stirred solution of NCS (1 equiv.) and pyridine (1 drop) in dry chloroform or 1,2-dichloroethane was added, in one portion, the oxime (1 equiv.). After stirring for 2 hours at 30-40°C the dipolarophile (2 equivs.) was added followed by slow addition of triethylamine in the same solvent, by means of a motorised syringe pump (7-14 hours). After the addition of the base was complete stirring was continued for 1 hour before washing the reaction mixture with water (x3), then drying the organic layer over $MgSO_4$. The residue, after evaporation of the solvent, was purified by flash column chromatography, recrystallisation, or both, to obtain the pure bis-heterocyclic adducts.

3.10.4.1. Cycloadducts of 5-phenylisoxazole-3-carbonitrile oxide.

3.10.4.1.1. 5-phenyl-3-(5-phenylisoxazol-3-yl)-2-isoxazoline (86).

Recrystallisation from methanol afforded clear needles (0.83 g, 54%), m.p. 143-144°C, δ_H (80 MHz; $CDCl_3$) 7.85-7.73 (2H, m, ArH), 7.50-7.32 (8H, m, ArH), 6.98 (1H, s, $H_{4\ isoxazole}$), 5.79 (1H, dd, J_{H5H4a} 10.9 Hz, J_{H5H4b} 8.9 Hz, $H_{5\ isoxazoline}$), 3.88 (1H, dd, J_{H4aH4b} 17.4 Hz, J_{H4aH5} 10.9 Hz, $H_{4a\ isoxazoline}$), 3.42 (1H, dd, J_{H4bH4a} 17.4 Hz, J_{H4bH5} 8.9 Hz, $H_{4b\ isoxazoline}$); δ_C (50 MHz; $CDCl_3$) 170.3, 155.5 (C_3, $C_{5\ isoxazole}$), 149.2 ($C_{3\ isoxazoline}$), 139.7 (PhC), 130.3, 128.2, 128.8, 128.6, 125.7, 125.6$_8$ (PhCH), 126.5 (PhC), 97.2 ($C_{4\ isoxazole}$), 83.4 ($C_{5\ isoxazoline}$), 41.5 ($C_{4\ isoxazoline}$).

3.10.4.1.2 5-octyl-3-(5-phenylisoxazol-3-yl)-2-isoxazoline (85).

Recrystallisation from ethanol (or hexane) afforded a white gelatinous mass, which after vacuum filtration left a white amorphous solid (0.72 g, 51%), m.p. 95.5-97°C, δ_H (80 MHz; $CDCl_3$) 7.84-7.67 (2H, m, ArH), 7.53-7.35 (3H, m, ArH), 6.91 (1H, s, $H_{4\ isoxazole}$), 5.0-4.6 (1H, m, $H_{5\ isoxazoline}$), 3.48 (1H, dd, J_{H4aH4b} 17.2 Hz, J_{H4aH5} 10.3 Hz, $H_{4a\ isoxazoline}$), 3.02 (1H, dd, J_{H4bH4a} 17.2 Hz, J_{H4bH5} 8.7 Hz, $H_{4b\ isoxazoline}$), 1.82-1.15 (14H, m, 7xCH_2), 0.87 (3H, br.t, CH_3); m/z 326 (M^+, 12%), 213 (100), 185 (51), 116 (26), 105 (92), 77 (50).

3.10.4.1.3. 5-*octyl*-3-(5-*phenylisoxazol*-3-*yl*)*isoxazole* (94).

Flash column chromatography (EtOAc/hexane, 3:97) afforded (94) as a white solid (0.34 g, 40%), m.p. 75-76°C (from methanol) (Found: C, 74.1; H, 7.50; N, 8.80. $C_{20}H_{24}N_2O_2$ requires C, 74.04; H, 7.46; N, 8.64%); δ_H (200 MHz; $CDCl_3$) 7.84-7.79 (2H, m, ArH), 7.52-7.45 (3H, m, ArH), 7.01 (1H, s, $H_{4\ isox\text{-}5\text{-}Ph}$), 6.53 (1H, s, $H_{4\ isox\text{-}5\text{-}octyl}$), 2.81 (2H, br.t, 5α-$CH_2$), 1.74

(2H, m, CH_2), 1.45-1.17 (10H, br.m, 5xCH_2), 0.87 (3H, br.t, CH_3); δ_C (50 MHz; $CDCl_3$) 174.8, 170.6, 154.9, 154.0 (C_3, $C_{3'}$, C_5, $C_{5'}$), 130.3, 128.9, 125.7 (PhCH), 126.7 (PhC), 98.9, 97.4 (C_4, $C_{4'}$), 31.6, 28.9, 27.2, 26.5, 22.4 (CH_2s), 13.9 (CH_3); m/z 324 (*M*+, 67%), 307 (24), 240 (91), 226 (100), 105 (86).

3.10.4.1.4. 5-*octadecyl*-3-(5-*phenylisoxazol*-3-*yl*)-2-*isoxazoline* **(93).**

Recrystallisation from ethanol followed by suction filtration of the gelatinous mass furnished **(93)** as a white amorphous solid (0.89 g, 72%), m.p. 100-102°C (Found: C, 77.1; H, 10.1; N, 5.93. $C_{30}H_{46}N_2O_2$ requires C, 77.20; H, 9.93; N, 6.00%); δ_H (80 MHz; $CDCl_3$) 7.84-7.72 (2H, m, ArH), 7.51-7.38 (3H, m, ArH), 6.91 (1H, s, $H_{4\ isoxazole}$), 5.02-4.57 (1H, m, $H_{5\ isoxazoline}$), 3.48 (1H, dd, J_{H4aH4b} 17.2 Hz, J_{H4aH5} 10.3 Hz, $H_{4a\ isoxazoline}$), 3.02 (1H, dd, J_{H4bH4a} 17.2 Hz, J_{H4bH5} 8.75 Hz, $H_{4b\ isoxazoline}$), 1.74-1.05 (34H, br.m, 17xCH_2), 0.80 (3H, br.t, CH_3); δ_C (50 MHz; $CDCl_3$) 170.4, 156.1 (C_3, $C_{5\ isoxazole}$), 149.4 ($C_{3\ isoxazoline}$), 130.4, 128.9, 125.8 (PhCH), 126.9 (PhC), 97.3 ($C_{4\ isoxazole}$), 82.7 ($C_{5\ isoxazoline}$), 38.8 ($C_{4\ isoxazoline}$), 35.0, 31.8, 29.5, 25.2, 22.5 (CH_2s), 13.9 (CH_3); m/z 466 (*M*+, 9%), 361 (13), 213 (100), 187 (14), 185 (22), 105 (61), 77 (18).

3.10.4.1.5. 4,5-di-(5-phenylisoxazol-3-yl)furazan-*N*-oxide **(65).**

To a stirred solution of NCS (0.28 g, 2.13 mmol) in chloroform (10 ml) was added 3-aldoximino-5-phenylisoxazole **(80a)** (0.40 g, 2.13 mmol). This was stirred at 40°C for 2 hours before adding triethylamine (0.24 g, 2.34 mmol) in chloroform (2 ml) over 2 minutes. After stirring for 1 hour the reaction mixture was washed with water (3 x 30 ml), dried over $MgSO_4$ and the solvent evaporated *in vacuo*, affording a yellowish solid.

Recrystallisation from benzene/hexane (4:1) furnished the title compound **(65)** as a white powder (0.17 g, 43%), m.p. 180-182°C (lit.,[129] 188°C); δ_H (80 MHz; $CDCl_3$) 7.92-7.76 (4H, m, ArH), 7.57-7.41 (6H, m, ArH), 7.31 (1H, s, H_4), 7.18 (1H, s, $H_{4'}$).

3.10.4.2. Cycloadducts of 5-octylisoxazole-3-carbonitrile oxide.

3.10.4.2.1. *5-phenyl-3-(octylisoxazol-3-yl)-2-isoxazoline* **(95).**

Flash column chromatography (hexane then EtOAc/hexane, 7:93) followed by recrystallisation from methanol afforded **(95)** as fine crystalline platelets (0.52 g, 72%), m.p. 46-47°C (found: M^+, 326.1998. $C_{20}H_{26}N_2O_2$ requires M, 326.19942); δ_H (80 MHz; $CDCl_3$) 7.34 (5H, br.s, ArH), 6.44 (1H, t, $J_{H4H\text{-}5\alpha}$ 0.8 Hz, $H_{4\ isoxazole}$), 5.75 (1H, dd, J_{H5H4a} 10.9 Hz, J_{H5H4b} 8.8 Hz, $H_{5\ isoxazoline}$), 3.82 (1H, dd, J_{H4aH4b} 17.4 Hz, J_{H4aH5} 10.9 Hz, $H_{4a\ isoxazoline}$), 3.36 (1H, dd, J_{H4bH4a} 17.4 Hz, J_{H4bH5} 8.8 Hz, $H_{4b\ isoxazoline}$), 2.76 (2H, br.t, 5α-CH_2), 1.81-1.10 (12H, m, 6xCH_2), 0.87 (3H, br.t, CH_3); δ_C (50 MHz; $CDCl_3$) 174.4, 155.0 (C_3, $C_{5\ isoxazole}$), 149.4 ($C_{3\ isoxazoline}$), 139.9 (PhC), 128.6, 128.2, 125.7 (PhCH), 98.7$_3$, 98.6$_9$ ($C_{4\ isoxazole}$) 83.2 ($C_{5\ isoxazoline}$), 41.7 ($C_{4\ isoxazoline}$), 31.6, 28.9, 27.2, 26.4, 22.4 (CH_2s), 13.9 (CH_3); m/z 326 (M^+, 69%), 115 (15), 104 (100), 91 (17), 77 (15).

3.10.4.2.2. 5-octyl-3-(5-octylisoxazol-3-yl)-2-isoxazoline **(84).**

Recrystallisation from methanol afforded **(84)** as a white powder (0.37 g, 57%), m.p. 60-61°C (Found: C, 72.7; H, 10.8; N, 7.74. $C_{22}H_{38}N_2O_2$ requires C, 72.88; H, 10.56; N, 7.73%); δ_H (80 MHz; $CDCl_3$) 6.36 (1H, t, $J_{H4(5\alpha\text{-}CH2)}$ 0.8 Hz, $H_{4\ isoxazole}$), 4.75-4.62 (1H, m, $H_{5\ isoxazoline}$), 3.41 (1H, dd, J_{H4aH4b}, 17.2 Hz, J_{H4aH5} 10.3 Hz, $H_{4a\ isoxazoline}$), 2.96 (1H, dd, J_{H4bH4a}

17.2 Hz, J_{H4bH5} 8.6 Hz, $H_{4b\ isoxazoline}$), 2.73 (2H, br.t, isoxazole 5α-CH_2), 1.76-1.08 (26H, br.m, 13xCH_2), 0.85 (3H, br.t, CH_3); δ_C (50 MHz; $CDCl_3$) 174.3, 155.5 (C_3, $C_{5\ isoxazole}$), 149.6 ($C_{3\ isoxazoline}$), 98.6 ($C_{4\ isoxazole}$), 82.4 ($C_{5\ isoxazoline}$), 38.7 ($C_{4\ isoxazoline}$), 35.0, 31.6, 29.3, 29.0, 27.2, 26.4, 25.2, 22.5 (CH_2s), 13.9 (CH_3); m/z 362 (*M*+, 8%), 249 (100), 221 (16), 81 (10).

3.10.4.2.3. *5-octadecyl-3-(5-octylisoxazole-3-yl)-2-isoxazoline* (**96**).

Flash column chromatography (hexane then EtOAc/hexane, 1:9) followed by recrystallisation from ethanol afforded (**96**) as a white amorphous solid (0.56 g, 62%), m.p. 74-76°C (Found: C, 76.02; H, 11.16; N, 5.52. $C_{32}H_{58}N_2O_2$ requires C, 76.43; H, 11.63; N, 5.57%); (Found: (*M*+H)+, 503.45766. $C_{32}H_{59}N_2O_2$ requires (*M*+H), 503.45763); δ_H (200 MHz; $CDCl_3$) 6.38 (1H, d, $H_{4\ isoxazole}$), 4.80-4.70 (1H, m, $H_{5\ isoxazoline}$), 3.41 (1H, dd, J_{H4aH4b} 17.2 Hz, J_{H4aH5} 10.6 Hz, $H_{4a\ isoxazoline}$), 3.00 (1H, dd, J_{H4bH4a} 17.2 Hz, J_{H4bH5} 8.3 Hz, $H_{4b\ isoxazoline}$), 2.74 (2H, br.t, isoxazole 5α-CH_2), 1.73-1.15 (46H, m, 23xCH_2), 0.86 (6H, br.t, 2xCH_3); δ_C (50 MHz; $CDCl_3$) 174.3, 155.4 (C_3, $C_{5\ isoxazole}$), 149.6 ($C_{3\ isoxazoline}$), 98.6 ($C_{4\ isoxazole}$), 82.4 ($C_{5\ isoxazoline}$), 38.8 ($C_{4\ isoxazoline}$), 35.0, 31.8, 31.7, 29.6, 29.3, 29.0, 27.3, 26.4, 25.2, 22.5 (CH_2s), 14.0 (CH_3s); m/z (FAB ms), 503 [(*M*+H)+].

3.10.4.2.4. *5-octyl-3-(5-octylisoxazol-3-yl)isoxazole* (**97**).

Flash column chromatography (hexane then EtOAc/hexane, 1:19) followed by recrystallisation from ethanol afforded (**97**) as fine white platelets (0.23 g, 36 %), m.p. 71-72°C (Found: C, 73.0; H, 10.1; N, 7.72. $C_{22}H_{36}N_2O_2$ requires C, 73.29; H, 10.06; N, 7.77%); δ_H (80 MHz; $CDCl_3$) 6.44 (2H, t, $J_{H4(5\alpha\text{-}CH2)}$ 0.8 Hz, H_4 &$H_{4'}$), 2.80 (4H, br.t, isoxazole 5α-CH_2), 1.77-1.26 (24H, m, 12xCH_2), 0.84 (6H, br.t, 2xCH_3);

δ_C (50 MHz; $CDCl_3$) 174.6, 154.3 (C_3, $C_{3'}$, C_5, $C_{5'}$), 98.9 (C_4, $C_{4'}$), 31.6, 29.0,28.9, 27.2, 26.5, 22.5 (CH_2s), 13.9 (CH_3s); m/z 360 (*M*+, 59%), 343 (37), 275 (68), 262 (100), 96 (36).

3.10.4.3. Cycloadduct of 4,5-dibutylisoxazole-3-carbonitrile oxide.

3.10.4.3.1 5-*octyl*-3-(4,5-*dibutylisoxazol*-3-*yl*)-2-*isoxazoline* (**99**).

Flash column chromatography (hexane then EtOAc/hexane, 2:98) furnished the title compound (**99**) as a clear oil (0.093 g, 57%), (Found: *M*+, 262.29260. $C_{22}H_{38}N_2O_2$ requires 262.29331); δ_H (200 MHz; $CDCl_3$) 4.70-4.58 (1H, m, H_5), 3.41 (1H, dd, J_{H4aH4b} 17.1 Hz, J_{H4aH5} 10.5 Hz, H_{4a}), 3.01 (1H, dd, J_{H4bH4a} 17.1 Hz, J_{H4bH5} 8.4 Hz, H_{4b}), 2.67 (2H, t, *J* 7.5 Hz, 5α-CH_2), 2.54 (2H, t, 4α-CH_2), 1.73-1.23 (22H, m, 11xCH_2), 0.94-0.80 (9H, CH_3); δ_C (90 MHz, $CDCl_3$) 169.9, 154.4 (C_3, $C_{5\ isoxazole}$), 150.3 ($C_{3\ isoxazoline}$), 113.8 ($C_{4\ isoxazole}$), 81.2 ($C_{5\ isoxazoline}$), 39.9 ($C_{4\ isoxazoline}$), 35.0, 31.8, 31.7, 29.6, 29.3, 29.2, 29.0, 25.3, 24.8, 22.5, 22.3, 22.1 (CH_2s), 13.9, 13.7, 13.5 (3xCH_3); m/z 362 (*M*+,13%), 333 (62), 249 (100), 191 (22), 177 (15), 85 (23).

3.10.4.4. Cycloadducts of 5-phenyl-2-isoxazoline-3-carbonitrile oxide.

3.10.4.4.1. (*RS/SR*)- and (*RR/SS*)-5-phenyl-3-(5-phenyl-2-isoxazolin-2-yl)-2-isoxazoline (**66a & b**).

Flash column chromatography (EtOAc/hexane, 1:19) furnished three compounds: the (*RS/SR*)-*meso*-cycloadduct (**66a**), a mixture of (**66a & 66b**), the (*RR/SS*)-cycloadduct (**66b**) (combined yield 46%) and unreacted 3-aldoximino-5-phenyl-2-isoxazoline (**80c**).

The first eluted component (**66a**) was isolated as a white crystalline solid (0.13 g, 21%), m.p. 169-172°C (from ethanol), (lit.,[129] 174-175°C); (Found:

M+, 292.1202. calc. for $C_{18}H_{16}N_2O_2$ *M*, 292.12117); δ_H (200 MHz; $CDCl_3$) 7.44-7.33 (10H, m, ArH), 5.74 (2H, dd, J_{H5H4a} 11.1 Hz, J_{H5H4b} 8.6 Hz, H_5 &$H_{5'}$), 3.75 (2H, dd, J_{H4aH4b} 17.3 Hz, J_{H4aH5} 11.1 Hz, H_{4a} & $H_{4a'}$), 3.35 (2H, dd, J_{H4bH4a} 17.3 Hz, J_{H4bH5} 8.6 Hz, H_{4b} & $H_{4b'}$); δ_C (50 MHz; $CDCl_3$) 150.6 (C_3 &$C_{3'}$), 139.7 (PhC), 128.6, 128.3, 125.7 (PhCH), 83.7 (C_5 & $C_{5'}$), 41.3 (C_4 & $C_{4'}$); m/z 292(*M*+, 98%), 115 (26), 104 (100), 77 (42).

The mixture of **(66a)** and **(66b)** was isolated as a crystalline solid (0.089 g, 15%), m.p. 93-100°C.

The third eluted component **(66b)** was isolated as a crystalline solid (0.062 g, 10%), m.p. 98-99°C (from ethanol), (lit.,[129] 96-97°C); (Found: *M*+, 292.1209. calc. for $C_{18}H_{16}N_2O_2$ *M*, 292.12117); δ_H (80 MHz; $CDCl_3$) 7.35 (10H, br.s, ArH), 5.74 (2H, dd, J_{H5H4a} 10.9 Hz, J_{H5H4b} 9.0 Hz, H_5 & $H_{5'}$), 3.76 (2H, dd, J_{H4aH4b} 17.1 Hz, J_{H4aH5} 10.9 Hz, H_{4a} & $H_{4a'}$), 3.31 (2H, dd, J_{H4bH4a} 17.1 Hz, J_{H4bH5} 9.0 Hz, H_{4b} & $H_{4b'}$), δ_C (50 MHz; $CDCl_3$) 150.6 (C_3 & $C_{3'}$), 139.7 (PhC), 128.7, 128.4, 125.8 (PhCH), 83.8 (C_5 & $C_{5'}$), 41.4 (H_4 & $H_{4'}$); m/z 292 (*M*+, 63%), 128 (18), 115 (24), 104 (77), 77 (42).

The fourth eluted component was unreacted 3-aldoximino-5-phenyl-2-isoxazoline **(80c)** (0.091 g, 23% recovery), m.p. 87-91°C, (from ethanol), δ_H (80 MHz; $CDCl_3$) 8.11 (2H, s, OH & HON=C*H*), 7.32 (5H, br.s, ArH), 5.67 (1H, dd, J_{H5H4a} 10.9 Hz, J_{H5H4b} 8.8 Hz, H_5), 3.58 (1H, ddd,J_{H4aH4b} 17.2 Hz, J_{H4aH5} 10.9 Hz, $J_{H4aH3\alpha}$ 0.7 Hz, H_{4a}), 3.12 (1H, ddd, J_{H4bH4a} 17.2 Hz, J_{H4bH5} 8.8 Hz, $J_{H4bH3\alpha}$ 0.7 Hz, H_{4b}).

3.10.4.4.2. (RR/SS)- and (RS/SR)-5-*octyl*-3-(5-*phenyl*-2-*isoxazolin*-3-*yl*)-2-*isoxazoline* **(100a & 100b)**[1]

The title compounds were isolated as a separable pair of racemic diastereomers in a combined yield of 53%. Separation was achieved by

flash column chromatography (EtOAc/hexane, 1:19). **(100a)** was recrystallised from methanol to yield an amorphous white solid (0.196 g, 28%), m.p. 78-79.5°C (Found: C, 72.97; H, 8.57; N, 8.34. $C_{20}H_{28}N_2O_2$ requires C, 73.1; H, 8.6; N, 8.5%); δ_H (200 MHz; $CDCl_3$) 7.42-7.27 (5H, m, ArH), 5.71 (1H, dd, J_{H5H4a} 11.1 Hz, J_{H5H4b} 8.6 Hz, H_5), 4.78-4.65 (1H, m, $H_{5'}$), 3.69 (1H, dd, J_{H4aH4b} 17.2 Hz, J_{H4aH5} 11.1 Hz, H_{4a}), 3.34 (1H, dd, $J_{H4a'H4b'}$ 17.0 Hz, $J_{H4a'H5'}$ 10.5 Hz, $H_{4a'}$), 3.28 (1H, dd, J_{H4bH4a} 17.2 Hz, J_{H4bH5} 8.6 Hz, H_{4b}), 2.94 (1H, dd, $J_{H4b'H4a'}$ 17.0 Hz, $J_{H4b'H5'}$ 8.4 Hz, $H_{4b'}$), 1.77-1.21 (14H, m, 7xCH_2), 0.88 (3H, t, CH_3); δ_C (50 MHz; $CDCl_3$) 150.9, 150.8 (C_3, $C_{3'}$), 139.8 (PhC), 128.6, 128.3, 125.7 (PhCH), 83.6, 82.9 (C_5, $C_{5'}$), 41.4 (C_4), 38.4 ($C_{4'}$), 35.0, 31.7, 29.2, 29.0, 25.1, 22.5 (CH_2s), 13.9 (CH_3); m/z 328 (*M*+, 100%), 215 (24), 130 (15), 115 (18), 105 (20), 91 (16), 77 (16).

(100b) was recrystallised from methanol to give fine white platelets (0.17 g, 25%), m.p. 69-70°C (Found: *M*+, 328.2149. $C_{20}H_{28}N_2O_2$ requires *M*, 328.21506); δ_H (200 MHz; $CDCl_3$) 7.41-7.31 (5H, m, ArH), 5.71 (1H, dd, J_{H5H4a} 11.1 Hz, J_{H5H4b} 8.7 Hz, H_5), 4.74 (1H, dddd, $J_{H5'H4a'}$ 10.5 Hz, $J_{H5'H4b'}$ 8.4 Hz, $J_{H5'CH_2}$ 5.9, 6.8 Hz, $H_{5'}$), 3.69 (1H, dd, J_{H4aH4b} 17.2 Hz, J_{H4aH5} 11.1 Hz, H_{4a}), 3.35 (1H, dd, $J_{H4a'H4b'}$ 17.1 Hz, $J_{H4a'H5'}$ 10.5 Hz, $H_{4a'}$), 3.29 (1H, dd, J_{H4bH4a} 17.2 Hz, J_{H4bH5} 8.7 Hz, H_{4b}), 2.94 (1H, dd, $J_{H4b'H4a'}$ 17.1 Hz, $J_{H4b'H5'}$ 8.5 Hz, $H_{4b'}$), 1.58-1.21 (14H, m, 7xCH_2), 0.88 (3H, t, CH_3); δ_C (50 MHz; $CDCl_3$) 151.0, 150.8 (C_3, $C_{3'}$), 139.8 (PhC), 128.7, 128.3, 125.8 (PhCH), 83.6, 83.0 (C_5, $C_{5'}$), 41.4 (C_4), 38.5 ($C_{4'}$), 35.0, 31.7, 29.3, 29.0, 25.2, 22.5 (CH_2s), 13.9 (CH_3); m/z 328 (*M*+, 86%), 215 (22), 129 (19), 115 (21), 105 (29), 104 (100), 91 (29), 77 (34).

1. Arbitrary assignment of stereochemistry.

3.10.4.5 Cycloadducts of 5-octyl-2-isoxazoline-3-carbonitrile oxide.

3.10.4.5.1. (*RR/SS*)- and (*RS/SR*)-5-octyl-3-(5-phenyl-2-isoxazolin-3-yl)-2-isoxazoline **(100a & 100b)**[1]

The title compounds **(100a & 100b)** were isolated as a separable pair of racemic diastereomers (0.152 g, 35%). Separation was achieved by flash column chromatography (EtOAc/hexane, 4:96) which gave three compounds.

3-formyl-5-octyl-2-isoxazoline **(79d)**; δ_H (200MHz; $CDCl_3$) 9.75 (1H, s, CHO), 4.91-4.75 (1H, m, H_5), 3.14 (1H, dd, J_{H4aH4b} 17.4 Hz, J_{H4aH5} 11.0 Hz, H_{4a}), 2.72 (1H, dd, J_{H4bH4a} 17.4 Hz, J_{H4bH5}, 8.5 Hz, H_{4b}), 1.75-1.26 (14H, m, 7xCH_2), 0.87 (3H, t, CH_3); δ_C (50 MHz; $CDCl_3$) 185.8 (CHO), 159.2 (C_3), 85.3 (C_5), 34.9 (C_4), 31.7, 29.2, 29.1, 29.0, 25.0, 22.5 (6xCH_2), 13.9 (CH_3); m/z 211 (*M*+, 14%).

(100a) was isolated as an amorphous white solid after recrystallisation from ethanol (0.069 g, 15%), m.p. 77-78°C, δ_H (200 MHz; $CDCl_3$) 7.41-7.30 (5H, m, ArH), 5.72 (1H, dd, J_{H5H4a} 11.1 Hz, J_{H5H4b} 8.6 Hz, H_5), 4.78-4.70 (1H, m, $H_{5'}$), 3.70 (1H, dd, J_{H4aH4b} 17.2 Hz, J_{H4aH5} 11.1 Hz, H_{4a}), 3.35 (1H, dd, $J_{H4a'H4b'}$ 17.1 Hz, $J_{H4a'H5'}$ 10.5 Hz, $H_{4a'}$), 3.30 (1H, dd, J_{H4bH4a} 17.2 Hz, J_{H4bH5} 8.6 Hz, H_{4b}), 2.94 (1H, dd, $J_{H4b'H4a'}$ 17.1 Hz, $J_{H4b'H5'}$ 8.4 Hz, $H_{4b'}$), 1.85-1.15 (14H, m, 7xCH_2), 0.88 (3H, t, CH_3); δ_C (50 MHz; $CDCl_3$) 151.0, 150.8 (C_3, $C_{3'}$), 139.8 (PhC), 128.7, 128.3, 125.8 (PhCH), 83.6, 83.0 (C_5, $C_{5'}$), 41.4 (C_4), 38.5 ($C_{4'}$), 35.0, 31.7, 29.3, 29.1, 25.2, 22.5 (CH_2s), 13.9 (CH_3); m/z 328 (*M*+, 69%), 215 (15), 129 (19), 115 (19), 105 (29), 104 (100), 91 (27), 77 (30).

(100b) was isolated as white waxy platelets after recrystallisation from ethanol (0.083 g, 18%), m.p. 68-69.5°C, δ_H (200 MHz; $CDCl_3$) 7.42-7.28 (5H, m, ArH), 5.71 (1H, dd, J_{H5H4a} 11.1 Hz, J_{H5H4b} 8.7 Hz, H_5), 4.79-4.66

(1H, m, $H_{5'}$), 3.69 (1H, dd, J_{H4aH4b} 17.2 Hz, J_{H4aH5} 11.1 Hz, H_{4a}), 3.35 (1H, dd, $J_{H4a'H4b'}$ 17.0 Hz, $J_{H4a'H5'}$ 10.5 Hz, $H_{4a'}$), 3.29 (1H, dd, J_{H4bH4a} 17.2 Hz, J_{H4bH5} 8.7 Hz, H_{4b}), 2.94 (1H, dd, $J_{H4b'H4a'}$ 17.0 Hz, $J_{H4b'H5'}$ 8.4 Hz, $H_{4b'}$), 1.75-1.20 (14H, m, 7xCH_2), 0.87 (3H, t, CH_3); δ_C (50 MHz, $CDCl_3$) 151.0, 150.8 (C_3, $C_{3'}$), 139.8 (PhC), 128.7, 128.3, 125.8 (PhCH), 83.6, 83.0 (C_5, $C_{5'}$), 41.4 (C_4), 38.5 ($C_{4'}$), 35.0, 31.7, 29.3, 29.2, 29.1, 25.2, 22.5 (CH_2s), 14.0 (CH_3); m/z 328 (M^+, 100%), 215 (24), 130 (20), 129 (25), 115 (26), 105 (37), 91 (32), 77 (34).

1. Arbitrary assignment of stereochemistry.

3.10.4.5.2. (RS/SR)- and (RR/SS)- 5-*octyl*-3-(5-*octylisoxazolin*-3-*yl*)-2-*isoxazoline* **(101a & 101b).**

Dry flash chromatography (EtOAc/hexane, 6:94) was used to separate the mixture of diastereomeric adducts **(101a & 101b)** from other reaction components. This afforded the title compounds as a white powder (0.376 g, 58%). Flash column chromatography (x2) (EtOAc/hexane, 4:6) on 110 mg of the mixture allowed complete separation of the isomeric adducts.

The first eluted isomer **(101a)** was isolated as fine white flakes m.p. 124-125°C (from hexane), (Found: C, 72.65; H, 11.10; N, 7.55. $C_{22}H_{40}N_2O_2$ requires C, 72.5; H, 11.1; N, 7.7%); δ_H (200 MHz; $CDCl_3$) 4.75-4.62 (2H, m, H_5 & $H_{5'}$), 3.30 (2H, dd, J_{H4aH4b} 17.0 Hz, J_{H4aH5} 10.5 Hz, H_{4a} & H_{4b}), 2.88 (2H, dd, J_{H4bH4a} 17.0 Hz, J_{H4bH5} 8.4 Hz, H_{4b} & $H_{4b'}$), 1.73-1.20 (28H, m, 14xCH_2), 0.87 (6H, t, 2xCH_3); δ_C (90 MHz; $CDCl_3$) 151.1 (C_3, $C_{3'}$), 82.8 (C_5, $C_{5'}$), 38.5 (C_4, $C_{4'}$), 35.0, 31.7, 29.3, 29.2, 29.0, 25.2, 22.5 (CH_2s), 13.9 (CH_3); m/z (FAB ms) 365 [(M+H)$^+$].

The slower eluting isomer **(101b)** was isolated as fine white flakes m.p. 113-114.5°C (from hexane); (Found: C, 72.62; H, 11.06; N, 7.49. $C_{22}H_{40}N_2O_2$ requires C, 72.5; H, 11.1; N, 7.7%);

δ_H (200 MHz: $CDCl_3$) 4.75-4.62 (2H, m, H_5 & $H_{5'}$), 3.29 (2H, dd, J_{H4aH4b} 17.0 Hz, J_{H4aH5} 10.5 Hz, H_{4a} & $H_{4a'}$), 2.89 (2H, dd, J_{H4bH4a} 17.0 Hz, J_{H4bH5} 8.4 Hz, H_{4b} & $H_{4b'}$), 1.74-1.20 (28H, m, 14xCH_2), 0.87 (6H, t, 2xCH_3); δ_C (90 MHz; $CDCl_3$) 151.2 (C_3, $C_{3'}$), 82.8 (C_5, $C_{5'}$), 38.5 (C_4, $C_{4'}$), 35.0, 31.7, 29.3_1, 29.2_6, 29.1, 25.2, 22.5 (CH_2s), 13.9 (CH_3s); m/z (FAB ms) 365 [$(M+H)^+$].

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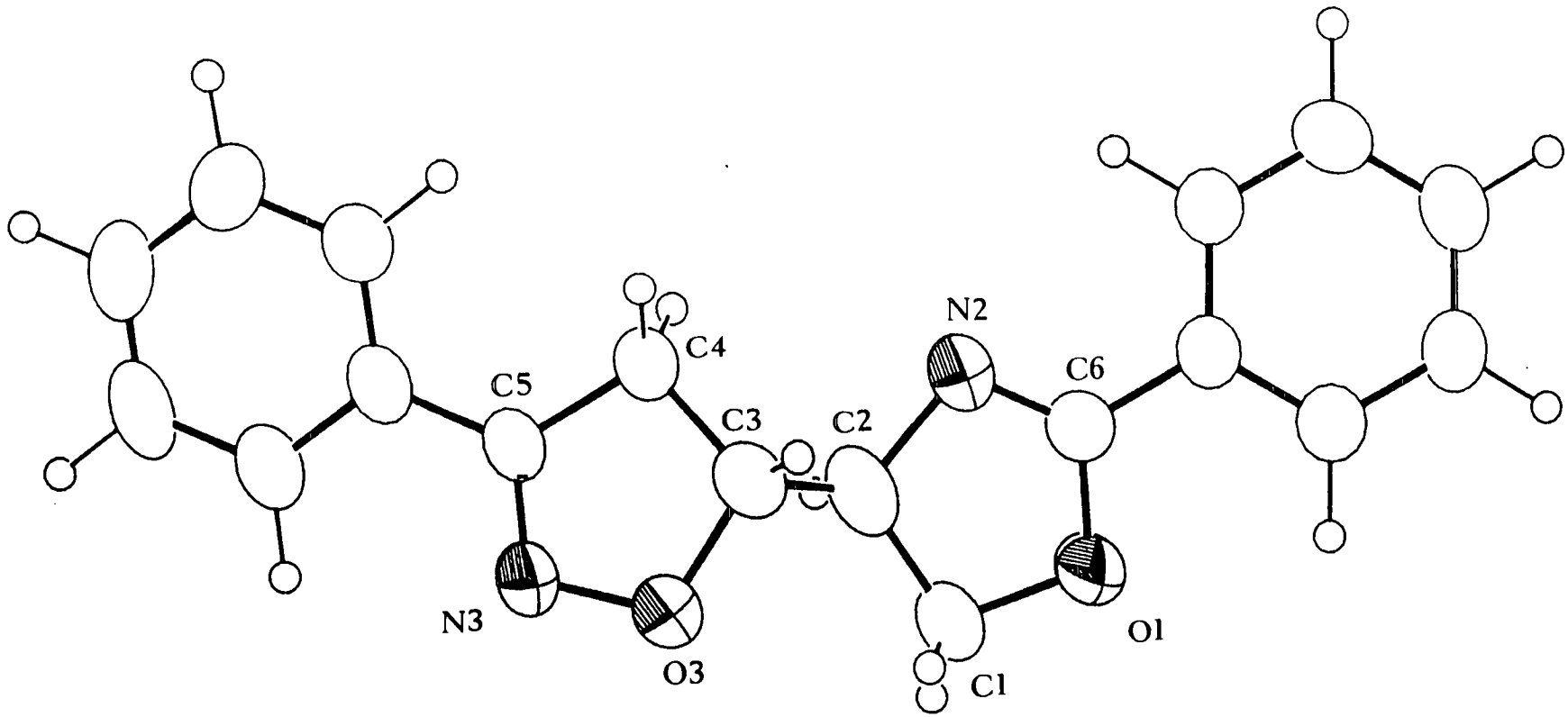


26a

Selected *X*-Ray Crystallographic Data for (26a)

Bond Lengths(Å) with standard deviations

O(1) - C(1)	1.454(7)	C(51P)-C(56P)	1.391(6)
O(1) - C(6)	1.357(6)	C(52P)-C(53P)	1.378(7)
N(2) - C(2)	1.494(7)	C(53P)-C(54P)	1.380(8)
N(2) - C(6)	1.276(6)	C(54P)-C(55P)	1.374(8)
C(1) - C(2)	1.538(8)	C(55P)-C(56P)	1.390(7)
C(2) - C(3)	1.428(8)	C(6) -C(61P)	1.450(6)
C(3) - C(4)	1.522(7)	C(61P)-C(62P)	1.401(6)
C(3) - O(3)	1.476(6)	C(61P)-C(66P)	1.386(6)
C(4) - C(5)	1.507(6)	C(62P)-C(63P)	1.379(6)
C(5) - N(3)	1.278(5)	C(63P)-C(64P)	1.383(7)
C(5) -C(51P)	1.461(6)	C(64P)-C(65P)	1.378(7)
O(3) - N(3)	1.410(5)	C(65P)-C(66P)	1.384(6)
C(51P)-C(52P)	1.405(6)		

Angles(degrees) with standard deviations

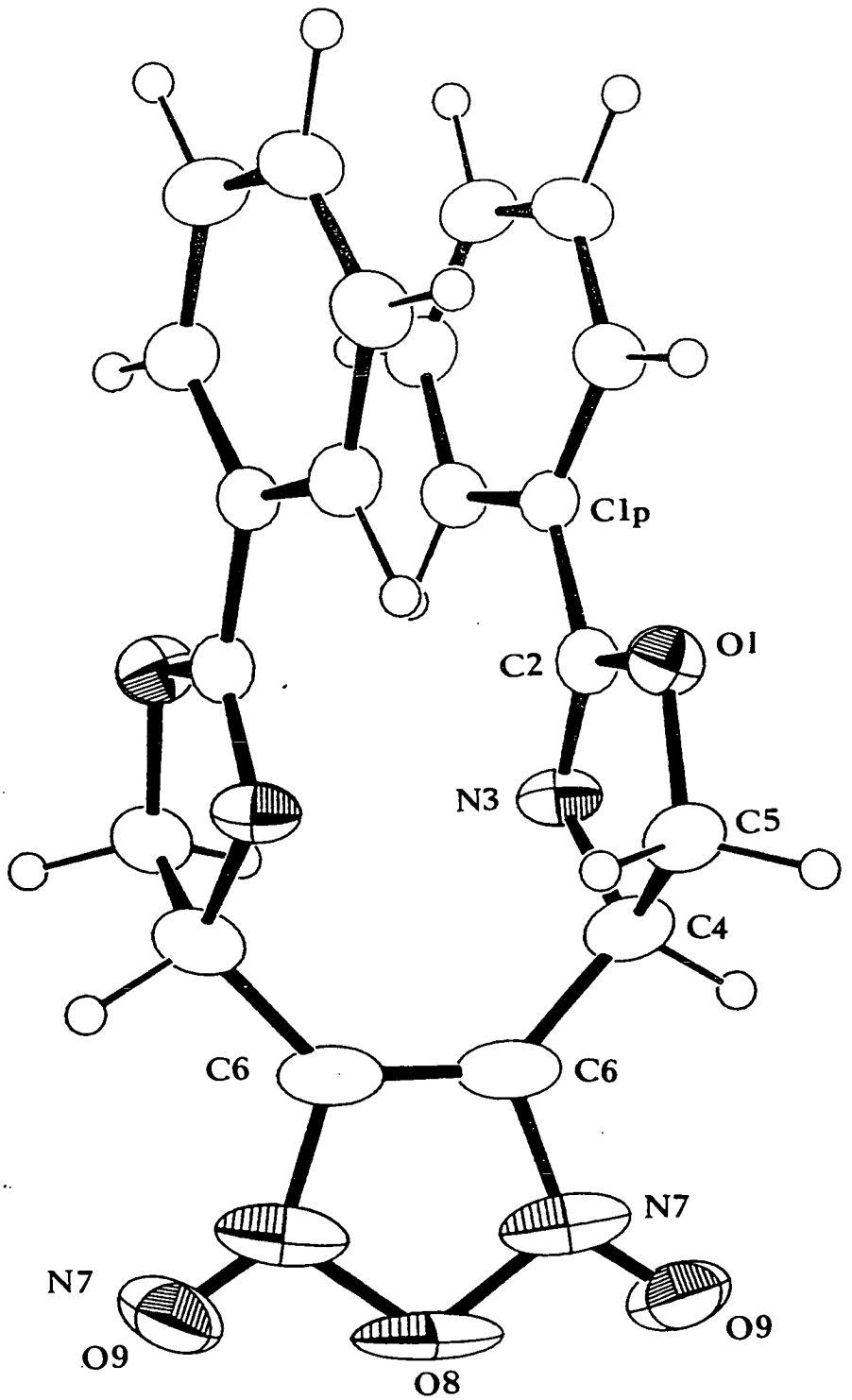
C(1) - O(1) - C(6)	106.3(4)	C(52P)-C(51P)-C(56P)	118.7(4)
C(2) - N(2) - C(6)	106.5(4)	C(51P)-C(52P)-C(53P)	120.5(4)
O(1) - C(1) - C(2)	103.7(4)	C(52P)-C(53P)-C(54P)	120.1(5)
N(2) - C(2) - C(1)	103.6(4)	C(53P)-C(54P)-C(55P)	120.1(5)
N(2) - C(2) - C(3)	111.7(5)	C(54P)-C(55P)-C(56P)	120.6(5)
C(1) - C(2) - C(3)	113.4(5)	C(51P)-C(56P)-C(55P)	120.0(4)
C(2) - C(3) - C(4)	118.4(5)	O(1) - C(6) - N(2)	118.1(4)
C(2) - C(3) - O(3)	108.2(4)	O(1) - C(6) -C(61P)	115.3(4)
C(4) - C(3) - O(3)	104.5(4)	N(2) - C(6) -C(61P)	126.6(4)
C(3) - C(4) - C(5)	101.7(4)	C(6) -C(61P)-C(62P)	119.5(4)
C(4) - C(5) - N(3)	114.2(4)	C(6) -C(61P)-C(66P)	120.9(4)
C(4) - C(5) -C(51P)	125.3(4)	C(62P)-C(61P)-C(66P)	119.6(4)
N(3) - C(5) -C(51P)	120.6(4)	C(61P)-C(62P)-C(63P)	119.0(4)
C(3) - O(3) - N(3)	109.8(3)	C(62P)-C(63P)-C(64P)	121.2(4)
C(5) - N(3) - O(3)	109.7(3)	C(63P)-C(64P)-C(65P)	119.8(4)
C(5) -C(51P)-C(52P)	120.8(4)	C(64P)-C(65P)-C(66P)	119.8(4)
C(5) -C(51P)-C(56P)	120.5(4)	C(61P)-C(66P)-C(65P)	120.6(4)

Torsion angles(degrees) with standard deviations

C(6) - O(1) - C(1) - C(2)	10.4(5)	N(3) - C(5) -C(51P)-C(52P)	-13.1(6)
C(1) - O(1) - C(6) - N(2)	-3.3(6)	N(3) - C(5) -C(51P)-C(56P)	165.9(4)
C(1) - O(1) - C(6) -C(61P)	178.2(4)	C(3) - O(3) - N(3) - C(5)	2.2(5)
C(6) - N(2) - C(2) - C(1)	11.7(5)	C(5) -C(51P)-C(52P)-C(53P)	179.0(4)
C(6) - N(2) - C(2) - C(3)	134.1(5)	C(56P)-C(51P)-C(52P)-C(53P)	0.0(6)
C(2) - N(2) - C(6) - O(1)	-5.8(6)	C(5) -C(51P)-C(56P)-C(55P)	-178.4(4)
C(2) - N(2) - C(6) -C(61P)	172.5(4)	C(52P)-C(51P)-C(56P)-C(55P)	0.6(6)
O(1) - C(1) - C(2) - N(2)	-13.2(5)	C(51P)-C(52P)-C(53P)-C(54P)	0.1(7)
O(1) - C(1) - C(2) - C(3)	-134.5(5)	C(52P)-C(53P)-C(54P)-C(55P)	-0.7(8)
N(2) - C(2) - C(3) - C(4)	69.5(6)	C(53P)-C(54P)-C(55P)-C(56P)	1.3(8)
N(2) - C(2) - C(3) - O(3)	-172.0(4)	C(54P)-C(55P)-C(56P)-C(51P)	-1.3(7)
C(1) - C(2) - C(3) - C(4)	-173.8(4)	O(1) - C(6) -C(61P)-C(62P)	178.4(4)
C(1) - C(2) - C(3) - O(3)	-55.4(6)	O(1) - C(6) -C(61P)-C(66P)	-1.8(6)
C(2) - C(3) - C(4) - C(5)	123.8(5)	N(2) - C(6) -C(61P)-C(62P)	0.1(7)
O(3) - C(3) - C(4) - C(5)	3.4(4)	N(2) - C(6) -C(61P)-C(66P)	179.9(4)
C(2) - C(3) - O(3) - N(3)	-130.6(4)	C(6) -C(61P)-C(62P)-C(63P)	179.9(4)
C(4) - C(3) - O(3) - N(3)	-3.6(5)	C(66P)-C(61P)-C(62P)-C(63P)	0.0(6)
C(3) - C(4) - C(5) - N(3)	-2.4(5)	C(6) -C(61P)-C(66P)-C(65P)	179.1(4)
C(3) - C(4) - C(5) -C(51P)	178.2(4)	C(62P)-C(61P)-C(66P)-C(65P)	-1.3(6)
C(4) - C(5) - N(3) - O(3)	0.2(5)	C(61P)-C(62P)-C(63P)-C(64P)	0.4(7)
C(51P)- C(5) - N(3) - O(3)	179.6(3)	C(62P)-C(63P)-C(64P)-C(65P)	0.1(7)
C(4) - C(5) -C(51P)-C(52P)	166.3(4)	C(63P)-C(64P)-C(65P)-C(66P)	-1.0(7)
C(4) - C(5) -C(51P)-C(56P)	-14.7(6)	C(64P)-C(65P)-C(66P)-C(61P)	1.5(7)

H-atom torsion angles(degrees) with standard deviations

C(6) - O(1) - C(1) -H(1A) 129.5(6)
C(6) - O(1) - C(1) -H(1B) -108.7(6)
C(6) - N(2) - C(2) - H(2) -109.4(6)
O(1) - C(1) - C(2) - H(2) 109.0(6)
H(1A) - C(1) - C(2) - N(2) -132.3(6)
H(1A) - C(1) - C(2) - H(2) -10.1(8)
H(1A) - C(1) - C(2) - C(3) 106.4(7)
H(1B) - C(1) - C(2) - N(2) 105.8(6)
H(1B) - C(1) - C(2) - H(2) -131.9(7)
H(1B) - C(1) - C(2) - C(3) -15.5(8)
N(2) - C(2) - C(3) - H(3) -47.5(6)
C(1) - C(2) - C(3) - H(3) 69.1(6)
H(2) - C(2) - C(3) - H(3) -169.8(6)
H(2) - C(2) - C(3) - C(4) -52.7(7)
H(2) - C(2) - C(3) - O(3) 65.7(6)
C(2) - C(3) - C(4) -H(4A) 5.0(7)
C(2) - C(3) - C(4) -H(4B) -117.5(6)
H(3) - C(3) - C(4) -H(4A) 120.1(6)
H(3) - C(3) - C(4) -H(4B) -2.4(7)
H(3) - C(3) - C(4) - C(5) -121.2(5)
O(3) - C(3) - C(4) -H(4A) -115.3(5)
O(3) - C(3) - C(4) -H(4B) 122.2(5)
H(3) - C(3) - O(3) - N(3) 114.0(6)
H(4A) - C(4) - C(5) - N(3) 116.3(5)
H(4A) - C(4) - C(5) -C(51P) -63.1(6)
H(4B) - C(4) - C(5) - N(3) -121.2(5)
H(4B) - C(4) - C(5) -C(51P) 59.4(6)
C(5) -C(51P)-C(52P)-H(52P) -0.9(7)
C(56P)-C(51P)-C(52P)-H(52P)-180.0(5)
C(5) -C(51P)-C(56P)-H(56P) 1.6(7)
C(52P)-C(51P)-C(56P)-H(56P)-179.3(5)
C(51P)-C(52P)-C(53P)-H(53P)-179.9(5)
H(52P)-C(52P)-C(53P)-H(53P) 0.0(8)
H(52P)-C(52P)-C(53P)-C(54P)-179.9(5)
C(52P)-C(53P)-C(54P)-H(54P) 179.3(6)
H(53P)-C(53P)-C(54P)-H(54P) -0.7(9)
H(53P)-C(53P)-C(54P)-C(55P) 179.3(6)
C(53P)-C(54P)-C(55P)-H(55P)-178.7(6)
H(54P)-C(54P)-C(55P)-H(55P) 1.3(9)
H(54P)-C(54P)-C(55P)-C(56P)-178.7(6)
C(54P)-C(55P)-C(56P)-H(56P) 178.7(5)
H(55P)-C(55P)-C(56P)-C(51P) 178.7(5)
H(55P)-C(55P)-C(56P)-H(56P) -1.3(8)
C(6) -C(61P)-C(62P)-H(62P) 0.0(7)
C(66P)-C(61P)-C(62P)-H(62P)-179.9(5)
C(6) -C(61P)-C(66P)-H(66P) -0.9(7)
C(62P)-C(61P)-C(66P)-H(66P) 179.0(5)
C(61P)-C(62P)-C(63P)-H(63P)-179.6(5)
H(62P)-C(62P)-C(63P)-H(63P) 0.3(8)
H(62P)-C(62P)-C(63P)-C(64P)-179.6(5)
C(62P)-C(63P)-C(64P)-H(64P)-179.9(5)
H(63P)-C(63P)-C(64P)-H(64P) 0.1(8)
H(63P)-C(63P)-C(64P)-C(65P)-179.8(5)
C(63P)-C(64P)-C(65P)-H(65P) 179.0(5)
H(64P)-C(64P)-C(65P)-H(65P) -1.0(8)
H(64P)-C(64P)-C(65P)-C(66P) 179.0(5)
C(64P)-C(65P)-C(66P)-H(66P)-178.5(5)
H(65P)-C(65P)-C(66P)-C(61P)-178.5(5)
H(65P)-C(65P)-C(66P)-H(66P) 1.5(8)



45b

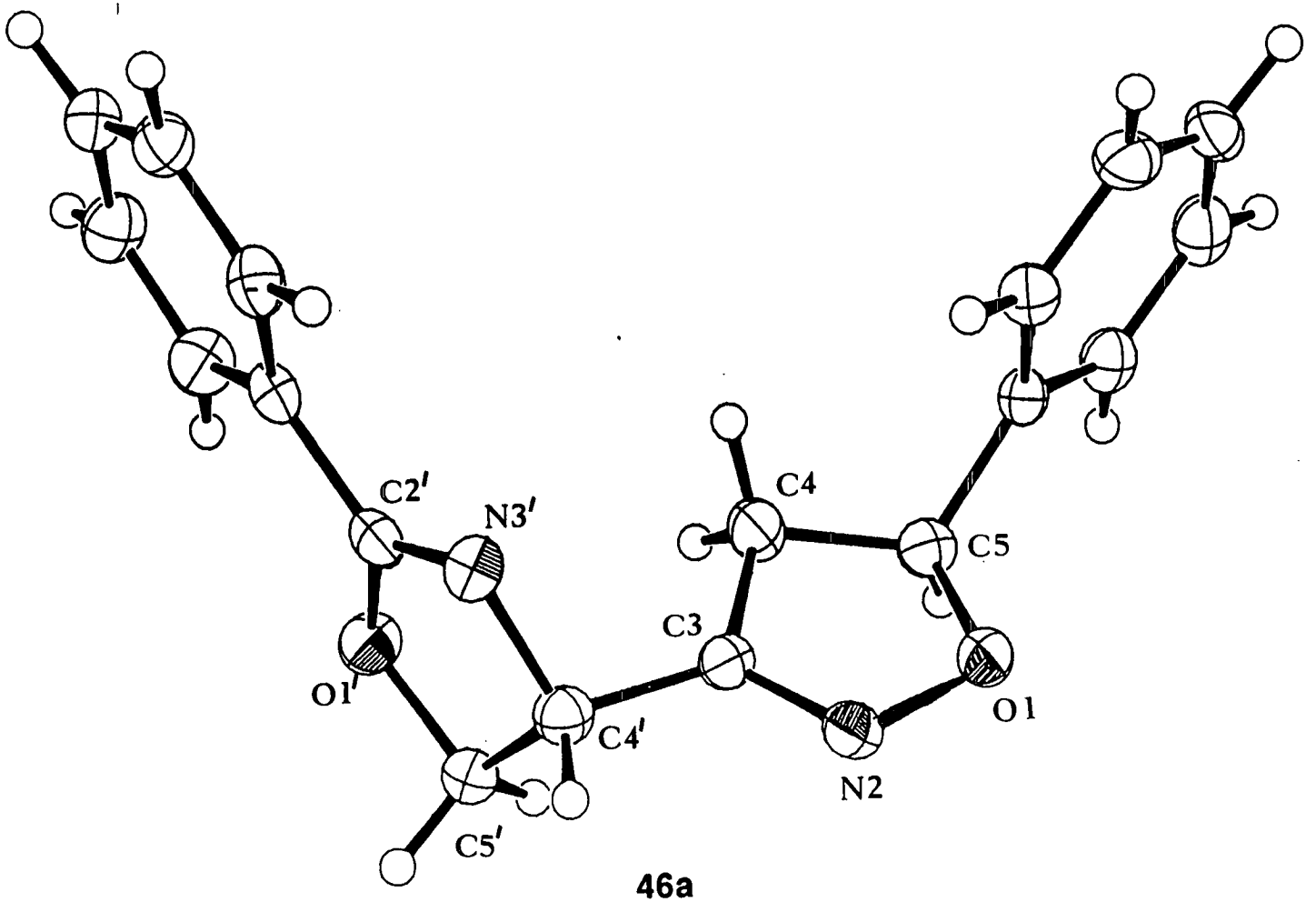
Selected *X*-Ray Crystallographic Data for (45b)

Bond Lengths(Å), angles(degrees) and torsion angles(degrees) with standard deviations

O(1) - C(2)	1.358(3)	N(7) - O(8)	1.408(4)
O(1) - C(5)	1.449(4)	N(7) - O(9)	1.065(7)
C(2) - N(3)	1.278(4)	C(1P) -C(2P)	1.388(4)
C(2) -C(1P)	1.467(4)	C(1P) -C(6P)	1.393(4)
N(3) - C(4)	1.475(4)	C(2P) -C(3P)	1.389(4)
C(4) - C(5)	1.546(4)	C(3P) -C(4P)	1.379(4)
C(4) - C(6)	1.492(5)	C(4P) -C(5P)	1.378(4)
C(6) -C(6')	1.417(5)	C(5P) -C(6P)	1.383(4)
C(6) - N(7)	1.316(5)		

C(2) - O(1) - C(5)	106.59(21)	C(6) - N(7) - O(8)	108.3(3)
O(1) - C(2) - N(3)	118.15(25)	C(6) - N(7) - O(9)	142.7(5)
O(1) - C(2) -C(1P)	116.04(23)	O(8) - N(7) - O(9)	108.8(4)
N(3) - C(2) -C(1P)	125.8(3)	C(2) -C(1P) -C(2P)	120.57(25)
C(2) - N(3) - C(4)	106.48(24)	C(2) -C(1P) -C(6P)	119.35(25)
N(3) - C(4) - C(5)	104.60(24)	C(2P) -C(1P) -C(6P)	120.1(3)
N(3) - C(4) - C(6)	112.0(3)	C(1P) -C(2P) -C(3P)	119.4(3)
C(5) - C(4) - C(6)	115.4(3)	C(2P) -C(3P) -C(4P)	120.3(3)
O(1) - C(5) - C(4)	103.19(23)	C(3P) -C(4P) -C(5P)	120.3(3)
C(4) - C(6) -C(6')	132.7(3)	C(4P) -C(5P) -C(6P)	120.1(3)
C(4) - C(6) - N(7)	118.8(3)	C(1P) -C(6P) -C(5P)	119.8(3)
C(6') - C(6) - N(7)	108.5(3)		

C(5) - O(1) - C(2) - N(3)	-4.3(3)	C(5) - C(4) - C(6) -C(6')	74.1(5)
C(5) - O(1) - C(2) -C(1P)	176.84(23)	C(5) - C(4) - C(6) - N(7)	-106.2(4)
C(2) - O(1) - C(5) - C(4)	8.5(3)	C(4) - C(6) - N(7) - O(8)	-178.7(3)
O(1) - C(2) - N(3) - C(4)	-2.5(3)	C(4) - C(6) - N(7) - O(9)	6.3(9)
C(1P) - C(2) - N(3) - C(4)	176.3(3)	C(6') - C(6) - N(7) - O(8)	1.1(4)
O(1) - C(2) -C(1P) -C(2P)	9.2(4)	C(6') - C(6) - N(7) - O(9)	-173.9(7)
O(1) - C(2) -C(1P) -C(6P)	-170.57(25)	C(2) -C(1P) -C(2P) -C(3P)	179.4(3)
N(3) - C(2) -C(1P) -C(2P)	-169.6(3)	C(2) -C(1P) -C(6P) -C(5P)	-179.9(3)
N(3) - C(2) -C(1P) -C(6P)	10.6(4)	C(6P) -C(1P) -C(2P) -C(3P)	-0.8(4)
C(2) - N(3) - C(4) - C(5)	7.7(3)	C(2P) -C(1P) -C(6P) -C(5P)	0.3(4)
C(2) - N(3) - C(4) - C(6)	133.3(3)	C(1P) -C(2P) -C(3P) -C(4P)	0.8(5)
N(3) - C(4) - C(5) - O(1)	-9.7(3)	C(2P) -C(3P) -C(4P) -C(5P)	-0.2(5)
C(6) - C(4) - C(5) - O(1)	-133.2(3)	C(3P) -C(4P) -C(5P) -C(6P)	-0.3(5)
N(3) - C(4) - C(6) -C(6')	-45.3(5)	C(4P) -C(5P) -C(6P) -C(1P)	0.3(4)
N(3) - C(4) - C(6) - N(7)	134.3(3)		



46a

Selected *X*-Ray Crystallographic Data for (46a)

Bond Lengths(A) with standard deviations

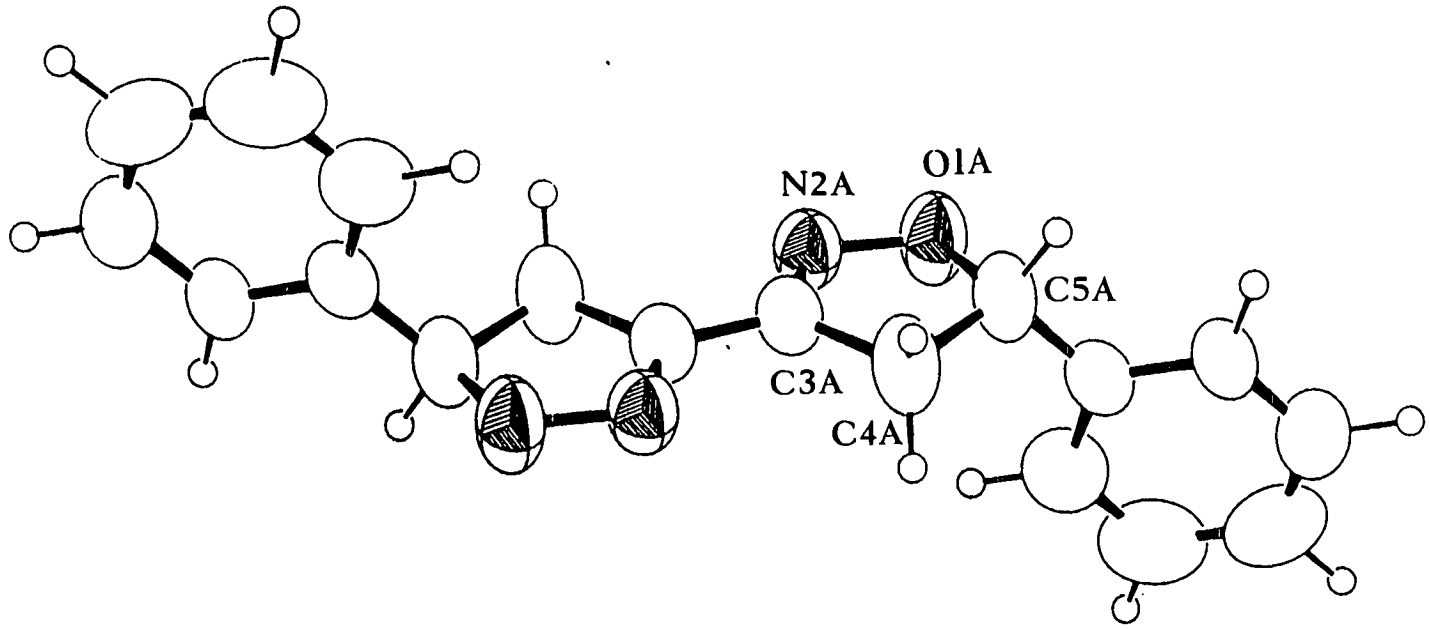
O(1) - N(2)	1.4204(24)	O(1') -C(2')	1.362(3)
O(1) - C(5)	1.476(3)	O(1') -C(5')	1.454(3)
N(2) - C(3)	1.274(3)	C(2') -N(3')	1.269(3)
C(3) - C(4)	1.492(3)	C(2') -C(2'1)	1.476(3)
C(3) -C(4')	1.501(3)	N(3') -C(4')	1.481(3)
C(4) - C(5)	1.512(4)	C(4') -C(5')	1.533(4)
C(5) -C(51)	1.503(3)	C(2'1)-C(2'2)	1.380(4)
C(51) -C(52)	1.387(3)	C(2'1)-C(2'6)	1.395(3)
C(51) -C(56)	1.381(3)	C(2'2)-C(2'3)	1.390(4)
C(52) -C(53)	1.383(4)	C(2'3)-C(2'4)	1.376(4)
C(53) -C(54)	1.378(4)	C(2'4)-C(2'5)	1.374(4)
C(54) -C(55)	1.377(4)	C(2'5)-C(2'6)	1.380(4)
C(55) -C(56)	1.389(4)		
C(4) -H(41)	0.98(3)	C(4') -H(4')	0.982(24)
C(4) -H(42)	1.00(3)	C(5') -H(5'1)	1.008(24)
C(5) - H(5)	0.978(23)	C(5') -H(5'2)	0.992(24)
C(52) -H(52)	0.936(24)	C(2'2)-H(2'2)	0.93(3)
C(53) -H(53)	0.88(3)	C(2'3)-H(2'3)	0.94(3)
C(54) -H(54)	0.96(3)	C(2'4)-H(2'4)	0.97(3)
C(55) -H(55)	0.98(3)	C(2'5)-H(2'5)	0.96(3)
C(56) -H(56)	0.99(3)	C(2'6)-H(2'6)	0.95(3)

Angles(degrees) with standard deviations

N(2) - O(1) - C(5)	108.91(16)	C(2') -O(1') -C(5')	105.29(17)
O(1) - N(2) - C(3)	109.05(18)	O(1') -C(2') -N(3')	118.78(20)
N(2) - C(3) - C(4)	114.46(20)	O(1') -C(2') -C(2'1)	115.33(19)
N(2) - C(3) -C(4')	121.39(20)	N(3') -C(2') -C(2'1)	125.82(21)
C(4) - C(3) -C(4')	124.15(20)	C(2') -N(3') -C(4')	105.96(19)
C(3) - C(4) - C(5)	101.62(20)	C(3) -C(4') -N(3')	108.53(19)
O(1) - C(5) - C(4)	104.13(19)	C(3) -C(4') -C(5')	111.56(20)
O(1) - C(5) -C(51)	108.26(19)	N(3') -C(4') -C(5')	104.19(19)
C(4) - C(5) -C(51)	116.84(20)	O(1') -C(5') -C(4')	103.42(19)
C(5) -C(51) -C(52)	120.70(21)	C(2') -C(2'1)-C(2'2)	121.43(21)
C(5) -C(51) -C(56)	120.29(21)	C(2') -C(2'1)-C(2'6)	119.21(21)
C(52) -C(51) -C(56)	118.99(21)	C(2'2)-C(2'1)-C(2'6)	119.32(22)
C(51) -C(52) -C(53)	120.50(23)	C(2'1)-C(2'2)-C(2'3)	120.22(24)
C(52) -C(53) -C(54)	120.18(25)	C(2'2)-C(2'3)-C(2'4)	120.16(24)
C(53) -C(54) -C(55)	119.77(25)	C(2'3)-C(2'4)-C(2'5)	119.77(24)
C(54) -C(55) -C(56)	120.12(25)	C(2'4)-C(2'5)-C(2'6)	120.73(24)
C(51) -C(56) -C(55)	120.40(23)	C(2'1)-C(2'6)-C(2'5)	119.80(23)
C(3) - C(4) -H(41)	113.1(15)	C(3) -C(4') -H(4')	109.8(14)
C(3) - C(4) -H(42)	110.3(15)	N(3') -C(4') -H(4')	110.8(14)
H(41) - C(4) -H(42)	106.2(22)	H(4') -C(4') -C(5')	111.8(14)
H(41) - C(4) - C(5)	112.9(15)	O(1') -C(5') -H(5'1)	107.0(14)
H(42) - C(4) - C(5)	112.9(15)	O(1') -C(5') -H(5'2)	105.6(14)
O(1) - C(5) - H(5)	108.6(14)	C(4') -C(5') -H(5'1)	115.3(14)
C(4) - C(5) - H(5)	110.0(14)	C(4') -C(5') -H(5'2)	112.4(14)
H(5) - C(5) -C(51)	108.7(14)	H(5'1)-C(5') -H(5'2)	112.1(20)
C(51) -C(52) -H(52)	120.8(15)	C(2'1)-C(2'2)-H(2'2)	122.6(17)
H(52) -C(52) -C(53)	118.7(15)	H(2'2)-C(2'2)-C(2'3)	117.1(17)
C(52) -C(53) -H(53)	121.3(17)	C(2'2)-C(2'3)-H(2'3)	119.9(16)
H(53) -C(53) -C(54)	118.5(17)	H(2'3)-C(2'3)-C(2'4)	119.9(16)
C(53) -C(54) -H(54)	121.2(15)	C(2'3)-C(2'4)-H(2'4)	119.2(15)
H(54) -C(54) -C(55)	119.0(15)	H(2'4)-C(2'4)-C(2'5)	121.0(15)
C(54) -C(55) -H(55)	121.2(16)	C(2'4)-C(2'5)-H(2'5)	121.5(16)
H(55) -C(55) -C(56)	118.7(16)	H(2'5)-C(2'5)-C(2'6)	117.7(16)
C(51) -C(56) -H(56)	121.2(16)	C(2'1)-C(2'6)-H(2'6)	117.0(16)
C(55) -C(56) -H(56)	118.4(16)	C(2'5)-C(2'6)-H(2'6)	123.2(16)

Torsion angles(degrees) with standard deviations

C(5) - O(1) - N(2) - C(3)	-7.19(23)	C(53) -C(54) -C(55) -C(56)	-1.3(4)
N(2) - O(1) - C(5) - C(4)	12.73(23)	C(54) -C(55) -C(56) -C(51)	-0.1(4)
N(2) - O(1) - C(5) -C(51)	137.71(18)	C(5') -O(1') -C(2') -N(3')	6.3(3)
O(1) - N(2) - C(3) - C(4)	-1.9(3)	C(5') -O(1') -C(2') -C(2'1)	-176.48(19)
O(1) - N(2) - C(3) -C(4')	178.95(19)	C(2') -O(1') -C(5') -C(4')	-12.99(22)
N(2) - C(3) - C(4) - C(5)	9.6(3)	O(1') -C(2') -N(3') -C(4')	4.1(3)
C(4') - C(3) - C(4) - C(5)	-171.21(21)	C(2'1)-C(2') -N(3') -C(4')	-172.88(22)
N(2) - C(3) -C(4') -N(3')	126.79(22)	O(1') -C(2') -C(2'1)-C(2'2)	-9.5(3)
N(2) - C(3) -C(4') -C(5')	-118.98(24)	O(1') -C(2') -C(2'1)-C(2'6)	172.72(20)
C(4) - C(3) -C(4') -N(3')	-52.3(3)	N(3') -C(2') -C(2'1)-C(2'2)	167.56(24)
C(4) - C(3) -C(4') -C(5')	61.9(3)	N(3') -C(2') -C(2'1)-C(2'6)	-10.3(4)
C(3) - C(4) - C(5) - O(1)	-12.69(23)	C(2') -N(3') -C(4') - C(3)	107.00(21)
C(3) - C(4) - C(5) -C(51)	-132.00(21)	C(2') -N(3') -C(4') -C(5')	-11.98(24)
O(1) - C(5) -C(51) -C(52)	-61.4(3)	C(3) -C(4') -C(5') -O(1')	-101.75(21)
O(1) - C(5) -C(51) -C(56)	117.16(23)	N(3') -C(4') -C(5') -O(1')	15.14(23)
C(4) - C(5) -C(51) -C(52)	55.7(3)	C(2') -C(2'1)-C(2'2)-C(2'3)	-177.40(23)
C(4) - C(5) -C(51) -C(56)	-125.76(25)	C(2'6)-C(2'1)-C(2'2)-C(2'3)	0.4(4)
C(5) -C(51) -C(52) -C(53)	176.82(23)	C(2') -C(2'1)-C(2'6)-C(2'5)	177.54(22)
C(56) -C(51) -C(52) -C(53)	-1.7(4)	C(2'2)-C(2'1)-C(2'6)-C(2'5)	-0.3(4)
C(5) -C(51) -C(56) -C(55)	-176.93(23)	C(2'1)-C(2'2)-C(2'3)-C(2'4)	-0.2(4)
C(52) -C(51) -C(56) -C(55)	1.6(4)	C(2'2)-C(2'3)-C(2'4)-C(2'5)	-0.2(4)
C(51) -C(52) -C(53) -C(54)	0.3(4)	C(2'3)-C(2'4)-C(2'5)-C(2'6)	0.3(4)
C(52) -C(53) -C(54) -C(55)	1.2(4)	C(2'4)-C(2'5)-C(2'6)-C(2'1)	0.0(4)
N(2) - O(1) - C(5) - H(5)	-104.5(14)	C(54) -C(55) -C(56) -H(56)	179.1(19)
N(2) - C(3) - C(4) -H(41)	130.9(17)	H(55) -C(55) -C(56) -C(51)	177.8(18)
N(2) - C(3) - C(4) -H(42)	-110.4(16)	H(55) -C(55) -C(56) -H(56)	-3.1(26)
C(4') - C(3) - C(4) -H(41)	-50.0(17)	C(2') -O(1') -C(5') -H(5'1)	-135.1(15)
C(4') - C(3) - C(4) -H(42)	68.8(16)	C(2') -O(1') -C(5') -H(5'2)	105.2(14)
N(2) - C(3) -C(4') -H(4')	5.5(15)	C(2') -N(3') -C(4') -H(4')	-132.3(15)
C(4) - C(3) -C(4') -H(4')	-173.6(15)	C(3) -C(4') -C(5') -H(5'1)	14.7(16)
C(3) - C(4) - C(5) - H(5)	103.5(15)	C(3) -C(4') -C(5') -H(5'2)	144.9(15)
H(41) - C(4) - C(5) - O(1)	-134.1(17)	N(3') -C(4') -C(5') -H(5'1)	131.6(15)
H(41) - C(4) - C(5) - H(5)	-17.9(22)	N(3') -C(4') -C(5') -H(5'2)	-98.2(15)
H(41) - C(4) - C(5) -C(51)	106.6(17)	H(4') -C(4') -C(5') -O(1')	134.8(15)
H(42) - C(4) - C(5) - O(1)	105.5(17)	H(4') -C(4') -C(5') -H(5'1)	-108.7(21)
H(42) - C(4) - C(5) - H(5)	-138.3(22)	H(4') -C(4') -C(5') -H(5'2)	21.5(21)
H(42) - C(4) - C(5) -C(51)	-13.8(17)	C(2') -C(2'1)-C(2'2)-H(2'2)	5.0(20)
H(5) - C(5) -C(51) -C(52)	-179.1(14)	C(2'6)-C(2'1)-C(2'2)-H(2'2)	-177.2(20)
H(5) - C(5) -C(51) -C(56)	-0.6(15)	C(2') -C(2'1)-C(2'6)-H(2'6)	-1.8(19)
C(5) -C(51) -C(52) -H(52)	-2.0(17)	C(2'2)-C(2'1)-C(2'6)-H(2'6)	-179.7(18)
C(56) -C(51) -C(52) -H(52)	179.4(17)	C(2'1)-C(2'2)-C(2'3)-H(2'3)	-179.8(19)
C(5) -C(51) -C(56) -H(56)	3.9(19)	H(2'2)-C(2'2)-C(2'3)-H(2'3)	-2.1(27)
C(52) -C(51) -C(56) -H(56)	-177.5(19)	H(2'2)-C(2'2)-C(2'3)-C(2'4)	177.6(19)
C(51) -C(52) -C(53) -H(53)	-178.8(20)	C(2'2)-C(2'3)-C(2'4)-H(2'4)	-176.5(17)
H(52) -C(52) -C(53) -H(53)	0.1(26)	H(2'3)-C(2'3)-C(2'4)-H(2'4)	3.2(26)
H(52) -C(52) -C(53) -C(54)	179.2(17)	H(2'3)-C(2'3)-C(2'4)-C(2'5)	179.5(19)
C(52) -C(53) -C(54) -H(54)	-178.0(18)	C(2'3)-C(2'4)-C(2'5)-H(2'5)	-176.1(18)
H(53) -C(53) -C(54) -H(54)	1.1(27)	H(2'4)-C(2'4)-C(2'5)-H(2'5)	0.1(26)
H(53) -C(53) -C(54) -C(55)	-179.7(19)	H(2'4)-C(2'4)-C(2'5)-C(2'6)	176.5(18)
C(53) -C(54) -C(55) -H(55)	-179.1(19)	C(2'4)-C(2'5)-C(2'6)-H(2'6)	179.3(20)
H(54) -C(54) -C(55) -H(55)	0.1(26)	H(2'5)-C(2'5)-C(2'6)-C(2'1)	176.4(18)
H(54) -C(54) -C(55) -C(56)	177.9(18)	H(2'5)-C(2'5)-C(2'6)-H(2'6)	-4.2(26)



66a

Selected *X*-Ray Crystallographic Data for (66a)

Bond Lengths(Å) with standard deviations

O(1A) -N(2A)	1.405(5)	O(1B) -N(2B)	1.409(5)
O(1A) -C(5A)	1.482(6)	O(1B) -C(5B)	1.480(6)
N(2A) -C(3A)	1.283(6)	N(2B) -C(3B)	1.274(6)
C(3A) -C(4A)	1.487(6)	C(3B) -C(4B)	1.495(7)
C(3A) -C(3A')	1.445(6)	C(3B) -C(3B")	1.449(6)
C(4A) -C(5A)	1.537(7)	C(4B) -C(5B)	1.525(7)
C(5A) -C(1PA)	1.485(5)	C(5B) -C(1PB)	1.480(6)

Angles(degrees) with standard deviations

N(2A) -O(1A) -C(5A)	109.9(3)	N(2B) -O(1B) -C(5B)	109.6(3)
O(1A) -N(2A) -C(3A)	109.3(4)	O(1B) -N(2B) -C(3B)	109.2(4)
N(2A) -C(3A) -C(4A)	115.1(4)	N(2B) -C(3B) -C(4B)	115.0(4)
N(2A) -C(3A) -C(3A')	118.7(4)	N(2B) -C(3B) -C(3B")	119.5(4)
C(4A) -C(3A) -C(3A')	126.1(4)	C(4B) -C(3B) -C(3B")	125.4(4)
C(3A) -C(4A) -C(5A)	101.4(4)	C(3B) -C(4B) -C(5B)	101.2(4)
O(1A) -C(5A) -C(4A)	104.0(4)	O(1B) -C(5B) -C(4B)	104.1(4)
O(1A) -C(5A) -C(1PA)	108.3(3)	O(1B) -C(5B) -C(1PB)	108.2(4)
C(4A) -C(5A) -C(1PA)	117.0(4)	C(4B) -C(5B) -C(1PB)	116.4(4)
C(5A) -C(1PA)-C(2PA)	119.8(3)	C(5B) -C(1PB)-C(2PB)	119.5(3)
C(5A) -C(1PA)-C(5PA)	120.2(3)	C(5B) -C(1PB)-C(6PB)	120.5(3)

Torsion angles(degrees) with standard deviations

C(5A) -O(1A) -N(2A) -C(3A)	2.3(5)	C(5B) -O(1B) -N(2B) -C(3B)	-4.3(5)
N(2A) -O(1A) -C(5A) -C(4A)	-5.1(4)	N(2B) -O(1B) -C(5B) -C(4B)	8.5(5)
N(2A) -O(1A) -C(5A) -C(1PA)	-130.2(3)	N(2B) -O(1B) -C(5B) -C(1PB)	132.9(4)
O(1A) -N(2A) -C(3A) -C(4A)	1.7(5)	O(1B) -N(2B) -C(3B) -C(4B)	-2.2(5)
O(1A) -N(2A) -C(3A) -C(3A')	-179.9(4)	O(1B) -N(2B) -C(3B) -C(3B")	-178.7(4)
N(2A) -C(3A) -C(4A) -C(5A)	-4.8(5)	N(2B) -C(3B) -C(4B) -C(5B)	7.3(5)
C(3A')-C(3A) -C(4A) -C(5A)	177.0(4)	C(3B")-C(3B) -C(4B) -C(5B)	-176.5(4)
N(2A) -C(3A) -C(3A')-C(4A')	1.9(7)	N(2B) -C(3B) -C(3B")-C(4B")	-3.9(7)
C(4A) -C(3A) -C(3A')-N(2A')	-1.9(7)	C(4B) -C(3B) -C(3B")-N(2B")	3.9(7)
C(3A) -C(4A) -C(5A) -O(1A)	5.5(4)	C(3B) -C(4B) -C(5B) -O(1B)	-8.9(5)
C(3A) -C(4A) -C(5A) -C(1PA)	124.8(4)	C(3B) -C(4B) -C(5B) -C(1PB)	-127.8(4)
O(1A) -C(5A) -C(1PA)-C(2PA)	56.5(4)	O(1B) -C(5B) -C(1PB)-C(2PB)	124.6(4)
O(1A) -C(5A) -C(1PA)-C(5PA)	-124.4(3)	O(1B) -C(5B) -C(1PB)-C(6PB)	-55.4(5)
C(4A) -C(5A) -C(1PA)-C(2PA)	-60.5(5)	C(4B) -C(5B) -C(1PB)-C(2PB)	-118.7(4)
C(4A) -C(5A) -C(1PA)-C(5PA)	118.7(4)	C(4B) -C(5B) -C(1PB)-C(6PB)	61.4(5)
C(5A) -C(1PA)-C(2PA)-C(3PA)	179.1(3)	C(5B) -C(1PB)-C(2PB)-C(3PB)	-179.9(3)
C(5A) -C(1PA)-C(5PA)-C(6PA)	-179.1(3)	C(5B) -C(1PB)-C(6PB)-C(5PB)	179.9(3)

H-atom torsion angles with standard deviations

N2A	O1A	C5A	H5A	113.557	0.509
N2A	C3A	C4A	H4A1	113.932	0.535
N2A	C3A	C4A	H4A2	-123.454	0.522
C3A	C4A	C5A	H5A	-119.028	0.481
H4A1	C4A	C5A	O1A	-113.185	0.484
H4A1	C4A	C5A	H5A	122.271	0.562
H4A1	C4A	C5A	C1PA	6.145	0.638
H4A2	C4A	C5A	O1A	124.200	0.473
H4A2	C4A	C5A	H5A	-0.336	0.664
H4A2	C4A	C5A	C1PA	-116.470	0.502
H5A	C5A	C1PA	C2PA	-179.014	0.393
H5A	C5A	C1PA	C5PA	0.141	0.561
C5A	C1PA	C2PA	H2PA	-0.838	0.500
C5PA	C1PA	C2PA	H2PA	-180.000	0.321
C5A	C1PA	C5PA	H6PA	0.850	0.501
C2PA	C1PA	C5PA	H6PA	-180.000	0.321
C1PA	C2PA	C3PA	H3PA	-179.914	0.321
H2PA	C2PA	C3PA	C4PA	179.926	0.321
H2PA	C2PA	C3PA	H3PA	0.000	0.517
C2PA	C3PA	C4PA	H4PA	179.914	0.321
H3PA	C3PA	C4PA	C6PA	-180.000	0.321
H3PA	C3PA	C4PA	H4PA	0.000	0.517
C3PA	C4PA	C6PA	H5PA	179.914	0.321
H4PA	C4PA	C6PA	C5PA	-179.921	0.321
H4PA	C4PA	C6PA	H5PA	0.000	0.517
C4PA	C6PA	C5PA	H6PA	179.914	0.321
H5PA	C6PA	C5PA	C1PA	-180.000	0.321
H5PA	C6PA	C5PA	H6PA	0.000	0.517
N2B	O1B	C5B	H5B	-110.421	0.533
N2B	C3B	C4B	H4B1	125.942	0.546
N2B	C3B	C4B	H4B2	-111.362	0.568
C3B	C4B	C5B	H5B	115.497	0.509
H4B1	C4B	C5B	O1B	-127.513	0.506
H4B1	C4B	C5B	H5B	-3.158	0.711
H4B1	C4B	C5B	C1PB	113.515	0.542
H4B2	C4B	C5B	O1B	109.789	0.524
H4B2	C4B	C5B	H5B	-125.856	0.597
H4B2	C4B	C5B	C1PB	-9.183	0.671
H5B	C5B	C1PB	C2PB	0.239	0.583
H5B	C5B	C1PB	C6PB	-179.701	0.419
C5B	C1PB	C2PB	H2PB	0.093	0.535
C6PB	C1PB	C2PB	H2PB	-179.912	0.348
C5B	C1PB	C6PB	H6PB	-0.082	0.543
C2PB	C1PB	C6PB	H6PB	-179.914	0.348
C1PB	C2PB	C3PB	H3PB	-180.000	0.348
H2PB	C2PB	C3PB	C4PB	-179.921	0.348
H2PB	C2PB	C3PB	H3PB	0.000	0.561
C2PB	C3PB	C4PB	H4PB	-180.000	0.348
H3PB	C3PB	C4PB	C5PB	179.921	0.348
H3PB	C3PB	C4PB	H4PB	0.000	0.561
C3PB	C4PB	C5PB	H5PB	-179.912	0.348
H4PB	C4PB	C5PB	C6PB	180.000	0.348
H4PB	C4PB	C5PB	H5PB	0.000	0.561
C4PB	C5PB	C6PB	H6PB	179.912	0.348
H5PB	C5PB	C6PB	C1PB	-179.921	0.348
H5PB	C5PB	C6PB	H6PB	0.000	0.561

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